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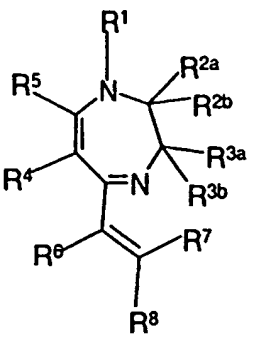
(54) Title: BENZODIAZEPINES AS INHIBITORS OF HPV E1 HELICASE



(I)

(57) Abstract: Described are novel benzodiazepin derivatives of general Formula (I). The novel compounds are inhibitors of the human papilloma virus (HPV) E1 helicase enzyme and can therefore be used as therapeutic agents for HPV mediated diseases.

Benzodiazepines as Inhibitors of HPV E1 Helicase

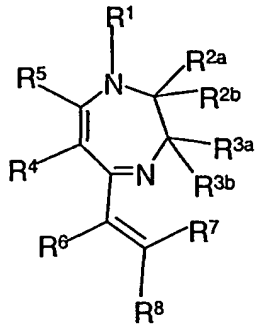
The invention is concerned with novel benzodiazepine derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds are inhibitors of the human papillomavirus E1 helicase enzyme which is involved in viral replication. Consequently the compounds of this invention may be advantageously used as therapeutic agents for HPV mediated processes.

Human papillomaviruses (HPV) are non-enveloped DNA viruses that induce hyperproliferative lesions of cutaneous and mucosal epithelia (warts).(Ref: P Howley – In Fields Virology 2nd Edn. Chap. 58 pp1625-1676 eds Fields et al Raven Press NY 1990) Genital HPV infection is one of the most common sexually transmitted diseases. (Ref Maw RD, Reitas M and Roy M, Int J STD + AIDS 9, 571-578, (1998)). It is estimated that visible genital warts are present in 1% of sexually active adults in the USA and that at least 15% have subclinical infection. (Koutsky L., Am. J. Med. 102, 3-8 (1997)). Over 90% of benign external warts (condyloma acuminata) are caused by HPV genotypes 6 and 11 (Handsfield H.H. Am. J. Med. 102, 16-27 (1997)).

E1 Helicase is the only known HPV enzyme and is essential for viral DNA replication. The E1 protein has been shown to possess ATPase and ATP-dependent DNA helicase catalytic activities. It is proposed to function as a hexameric helicase and sequence homology classifies it as a member of helicase superfamily III (other members: SV40 TAg, parvovirus NS1). Inhibition of the ATPase or helicase functions of this enzyme would be predicted to result in inhibition of HPV DNA replication.

The object of the present invention is to provide novel compounds which are potent inhibitors of the ATPase activity of the helicase enzyme and which accordingly show a potential to be efficacious as antiviral drugs.

This object could be achieved with the novel compounds of formula I as defined by general formula



I

wherein

R^1 is H, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl,

lower alkyl carbonyl, aryl carbonyl, lower alkyl amino carbonyl, aryl amino carbonyl,

lower alkoxy carbonyl,

aryloxy carbonyl,

R^{2a}, R^{2b} independently are H or lower alkyl or

R^{2a} and R^{2b} together are oxo,

R^1 and R^{2a} or R^{2b} together with the nitrogen and the carbon atom to which they are attached

form an optionally substituted heterocycle;

R^{3a}, R^{3b} independently are H or lower alkyl

R^4 and R^5 together with the two carbon atoms to which they are attached form optionally

substituted aryl or a optionally substituted heterocycle,

R^6 and R^7 is H or lower alkyl and

R^8 is optionally substituted aryl or heterocyclyl.

The term "lower" used in combination with alkyl and alkoxy defines an optionally substituted straight chained or branched alkyl chain carrying 1 to 6 carbon atoms,

preferably 1 to 4 carbon atoms. The term "lower" used in combination with alkenyl and alkynyl defines an optionally substituted straight chained or branched alkenyl or alkynyl chain carrying 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms.

Lower alkyl in R^1,R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 accordingly preferably stands for methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and tert.-butyl.

Lower alkoxy in R^1 preferably stands for methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy and tert.-butoxy.

Lower alkenyl in R^1 accordingly preferably is vinyl, 1-propenyl, 2-propenyl, i-propenyl and butenyl and its isomers.

Lower alkynyl in R^1 accordingly preferably is ethynyl, propynyl and its isomers and butynyl and its isomers.

Preferred meaning for R^1 is methyl.

Preferred meaning for R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 is hydrogen.

Suitable substituents of an alkyl chain can be selected from one or more of

aryl, heterocyclyl,

carboxyl, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxyl,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino
alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino,
nitro,

alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,

thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

halogen.

In all cases above where there are NH groups, the free hydrogen may also be substituted , preferably with lower alkyl. Examples are alkyl carbonyl (lower alkyl) amino, cycloalkyl (lower alkyl) amino carbonyl or alkoxy carbonyl (lower alkyl) amino.

Cycloalkyl has the meaning of an optionally substituted cycloalkyl group containing 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or adamantyl which can also be benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle, e.g. to phenyl.

The term aryl denotes optionally substituted phenyl and naphthyl, both optionally benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle e.g. to cyclohexyl or cyclopentyl.

The term heterocyclyl stands for an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, oxygen and sulfur which can also be benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic carbocycle or heterocycle.

Examples of suitable heterocycles are oxazolyl, isoxazolyl, furyl, tetrahydrofuryl, 1,3-dioxolanyl, dihydropyranyl, thienyl, pyrazinyl, isothiazolyl isoquinolinyl, indolyl, indazolyl, quinolinyl, dihydrooxazolyl, pyrimidinyl, benzofuranyl,

tetrazolyl, pyrrolidinonyl, (N-oxide)-pyridinyl, pyrrol, triazolyl e.g. 1,2,4-triazolyl, pyrazolyl, benzotriazolyl, priperidinyl, morpholinyl, thiazolyl, pyridinyl, dihydrothiazolyl, imidazolidinyl, pyrazolinyl, benzothienyl, piperazinyl, imidazolyl, thia diazolyl e.g. 1,2,3-thiadiazolyl, and benzothiazolyl.

Suitable substituents for cycloalkyl, aryl, heterocyclyl can be selected from those named for alkyl, in addition however lower alkyl, lower alkenyl and lower alkynyl are substituents to be added to the selection.

The term halogen stands for fluorine, chlorine, bromine and iodine.

R^4 and R^5 together with the two carbon atoms to which they are attached preferably form optionally substituted aryl , more preferably form optionally substituted phenyl.

R^8 preferably stands for optionally substituted aryl , more preferably for optionally substituted phenyl.

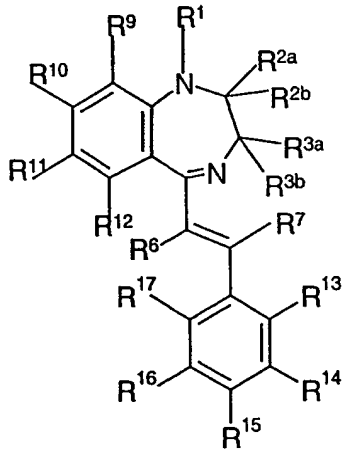
Any functional (i.e. reactive) group present in a side-chain may be protected, with the protecting group being a group which is known per se, for example, as described in "Protective Groups in Organic Synthesis", 2nd Ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. For example, an amino group can be protected by a tert.-butoxycarbonyl (BOC), formyl, trityl, benzyloxycarbonyl (Z), 9-fluorenylmethyloxcarbonyl (FMOC), trifluoroacetyl, 2-(biphenylyl)isopropoxycarbonyl or isobornyloxycarbonyl group or in the form of a phthalimido group; or a hydroxyl group can be protected by a tert. butyldimethylsilyl, tetrahydropyranyl, 4-methoxybenzyl, or benzyl; or a carboxyl group can be protected in the form of an ester, for example as a methyl or tert. butyl ester. The protecting group may be retained in the final compound or optionally be removed by techniques known in the art.

The compounds of this invention may contain one or more asymmetric carbon atoms and may therefore occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Furthermore, where a compound of the invention contains an olefinic double bond, this can have the (E) or (Z) configuration. Also, each chiral centre may be of the R or S

configuration. All such isomeric forms of these compounds are embraced by the present invention.

Compounds of formula (I) which are acidic can form pharmaceutically acceptable salts with bases such as alkali metal hydroxides, e.g. sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxides, e.g. calcium hydroxide, barium hydroxide and magnesium hydroxide, and the like; with organic bases e.g. N-ethyl piperidine, dibenzylamine, and the like. Those compounds of formula (I) which are basic can form pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric acid and hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid, and the like, and with organic acids, e.g. with acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid and p-toluene sulphonic acid, and the like. The formation and isolation of such salts can be carried out according to methods known in the art.

Preferred compounds of formula (I) are those having the formula



II

wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 are as above and

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are H, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl,

aryl, heterocyclyl,

carboxyl, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxyl,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino, alkyl carbonyl amino alkyl carbonyl amino, dialkyl amino carbonyl amino alkyl carbonyl amino, cycloalkyl carbonyl amino alkyl carbonyl amino, aryl carbonyl amino alkyl carbonyl amino, heterocyclyl carbonyl amino alkyl carbonyl amino,

alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino,
nitro,

alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,

thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

halogen

or

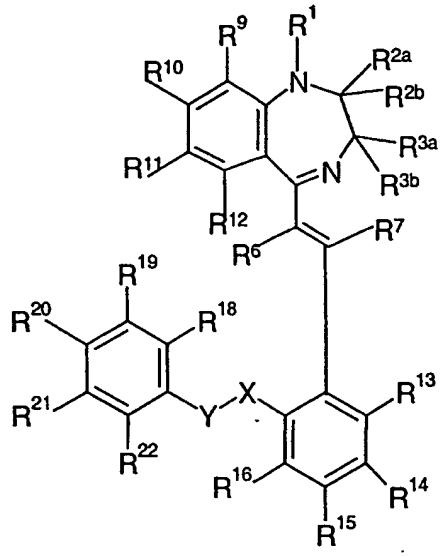
R^{10} and R^{11} together with the two carbon atoms to which they are attached form optionally

substituted aryl or an optionally substituted heterocycle.

Preferred meaning for R^1 is methyl.

Preferred meaning for R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 is hydrogen.

More preferred compounds of formula (I) are those having the formula



III

wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are as above and wherein

X is $(CH_2\text{-})_n$ with n being an integer between 0 and 3, -S-, -O- or $-NR^{23}$, wherein R^{23} is H or lower alkyl,

Y is $-(CH_2\text{-})_n$ with n being an integer between 0 and 3, and when X is $(CH_2\text{-})_n$ with n being an integer between 0 and 3 then Y is S, O or $-NR^{23}$ wherein R^{23} is as above,

R^{18}, R^{19}, R^{20} and R^{22} independently are H, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl,

aryl, heterocyclyl,

carboxyl, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxyl,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino, alkyl carbonyl amino alkyl carbonyl amino, dialkyl amino carbonyl amino alkyl carbonyl amino, cycloalkyl carbonyl amino alkyl carbonyl amino, aryl carbonyl amino alkyl carbonyl amino, heterocyclyl carbonyl amino alkyl carbonyl amino, alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino, nitro,
alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,
thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

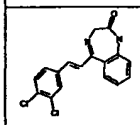
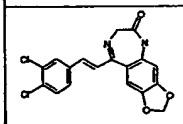
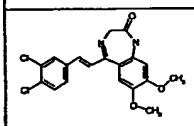
halogen.

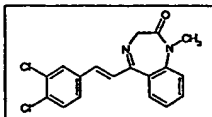
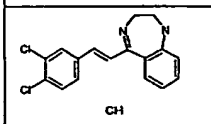
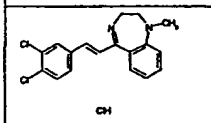
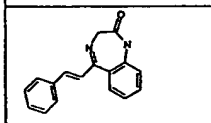
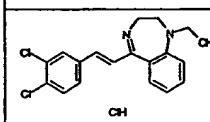
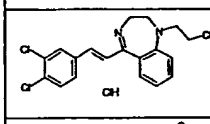
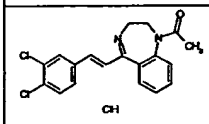
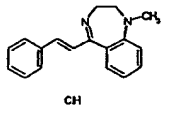
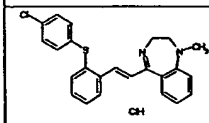
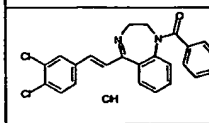
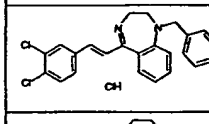
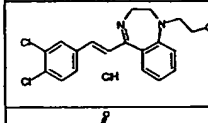
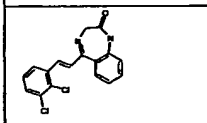
Preferred meaning for R^1 is methyl.

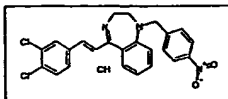
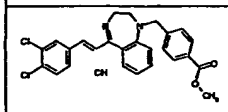
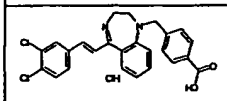
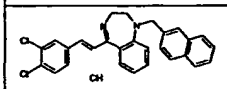
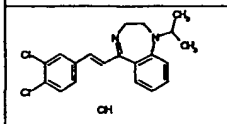
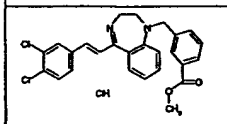
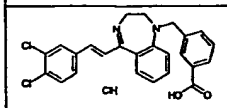
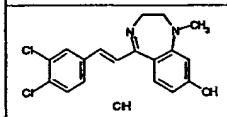
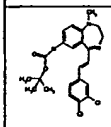
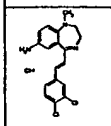
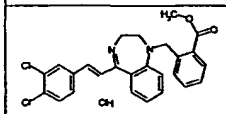
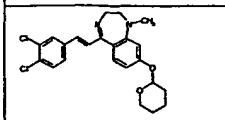
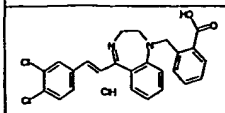
Preferred meaning for R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 is hydrogen.

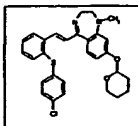
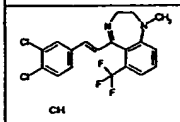
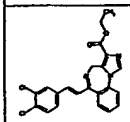
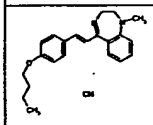
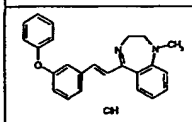
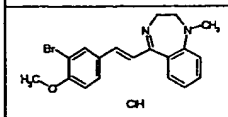
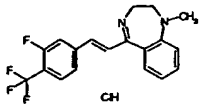
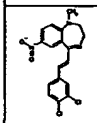
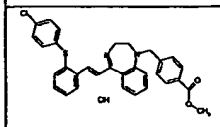
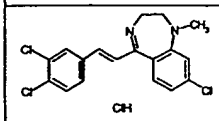
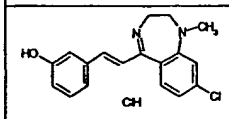
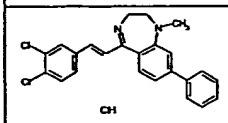
Examples of compounds of formula I are set out below in table A:

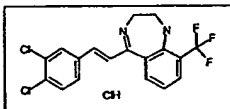
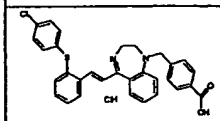
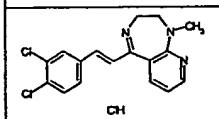
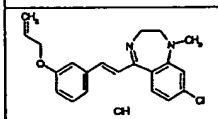
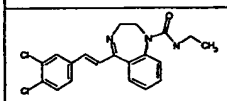
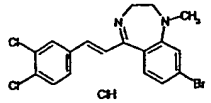
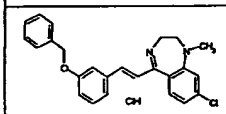
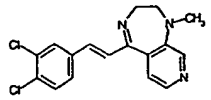
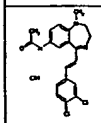
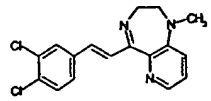
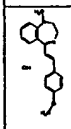
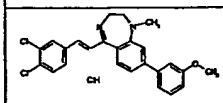
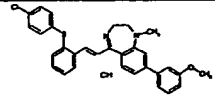
Table A:

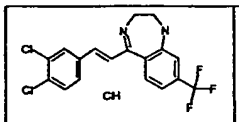
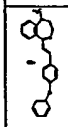
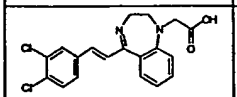
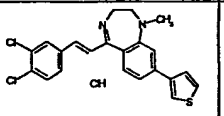
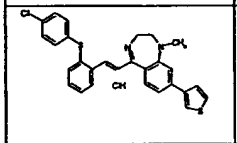
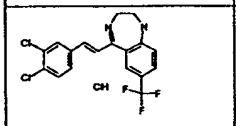
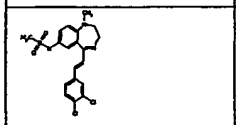
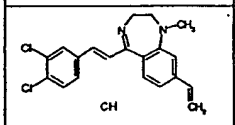
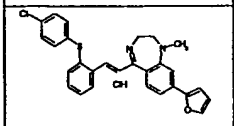
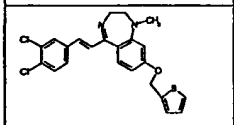
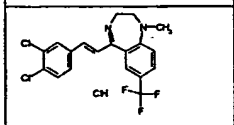
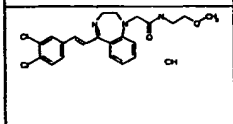
Structure	Names
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-2H-benzo-1,4-diazepin-2-one
	(E)-9-(3,4-Dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo [4,5-h][1,4]benzodiazepin-6-one
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-7,8-dimethoxy-2H-1,4-benzodiazepin-2-one

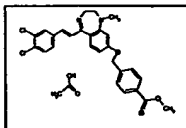
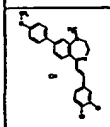
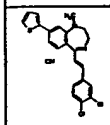
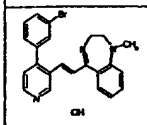
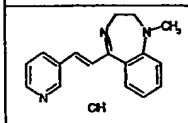
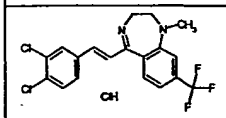
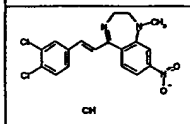
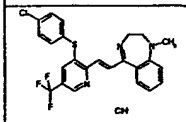
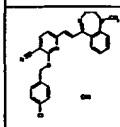
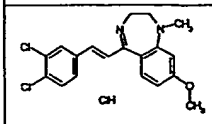
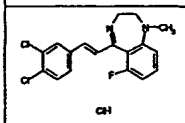
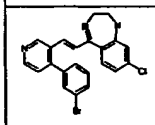
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-1-methyl-2H-benzo-1,4-diazepin-2-one
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-benzo-1,4-diazepine dihydrochloride
	(E)-1,3-Dihydro-5-styryl-2H-benzo-1,4-diazepin-2-one
	(E)-5-(3,4-Dichlorostyryl)-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-propyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-1-Acetyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-styryl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-1-Benzoyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-1-Benzyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-ethanol hydrochloride
	(E)-5-(2,3-Dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

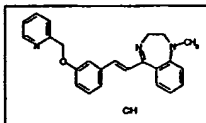
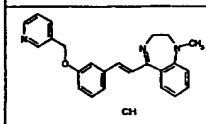
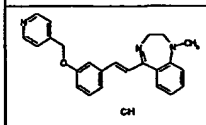
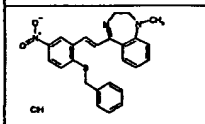
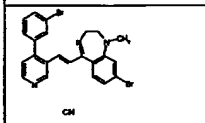
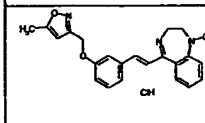
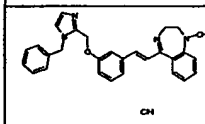
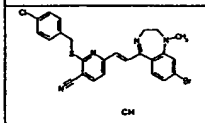
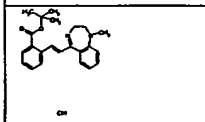
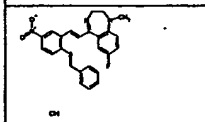
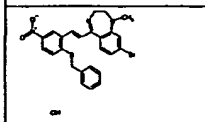
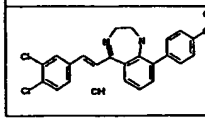
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-(4-nitrobenzyl)-1H-1,4-benzodiazepine dihydrochloride
	Methyl (E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate dihydrochloride
	(E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-[(2-naphthyl)methyl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-isopropyl-1H-1,4-benzodiazepine dihydrochloride
	Methyl (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-3-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-ol hydrochloride
	tert-Butyl (E)-[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]carbamate
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride
	Methyl (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(tetrahydro-2(RS)- pyranyloxy)-1-methyl-1H-1,4-benzodiazepine
	(E)-2-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride

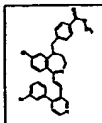
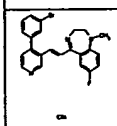
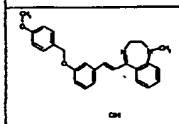
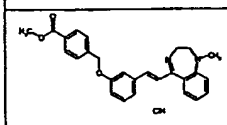
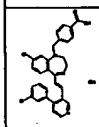
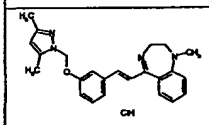
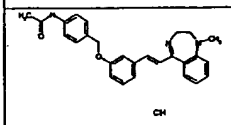
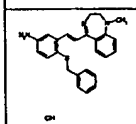
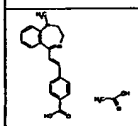
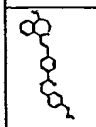
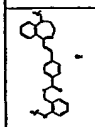
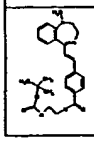
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-6-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	Ethyl (E)-6-(3,4-dichlorostyryl)-4H-imidazo[1,5-a][1,4]benzo-diazepine-3-carboxylate
	(E)-5-(4-Butoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(3-phenoxystyryl)-1H-1,4-benzo-diazepine dihydrochloride
	(E)-5-(3-Bromo-4-methoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-Fluoro-4-(trifluoromethyl)styryl]-2,3-dihydro-1-methyl-1H-benzo[e][1,4]diazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-7-nitro-1H-1,4-benzodiazepine
	Methyl (E)-4-[[5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-8-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-3-[2-(8-Chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl) vinyl]phenol hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-phenyl-1H-1,4-benzodiazepine dihydrochloride

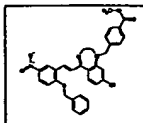
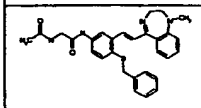
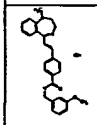
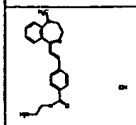
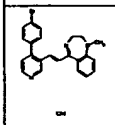
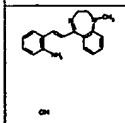
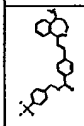
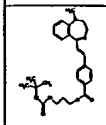
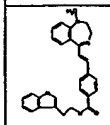
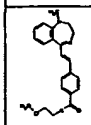
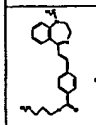
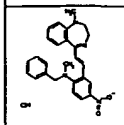
	(E)-5-(3,4-Dichlorostyryl)-9-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-4-[[5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzo-diazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[2,3-e][1,4] diazepine hydrochloride (1:3)
	(E)-5-(3-Allyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzo-diazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-N-ethyl-2,3-dihydro-1H-1,4-benzodiazepine-1-carboxamide
	(E)-8-Bromo-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3-Benzyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,4-e][1,4] diazepine
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-acetamide hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,2-e][1,4] diazepine
	(E)-2,3-Dihydro-5-(4-methoxystyryl)-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(3-methoxy-phenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride

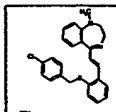
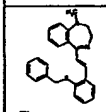
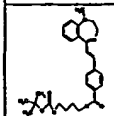
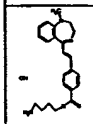
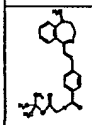
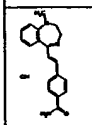
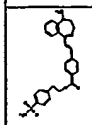
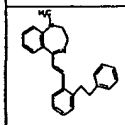
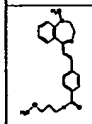
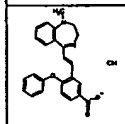
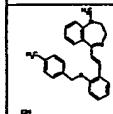
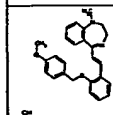
	(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(4-phenoxystyryl)-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-8-(3-thienyl)- 1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-N-[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]methanesulfonamide
	5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-vinyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-8-(2-furyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thenyloxy)-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-N-(2-methoxyethyl)-1H-1,4-benzodiazepin-1-acetamide dihydrochloride

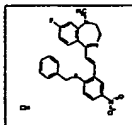
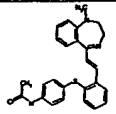
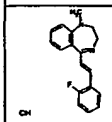
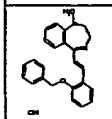
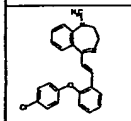
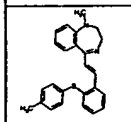
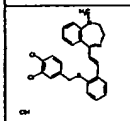
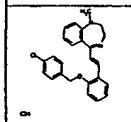
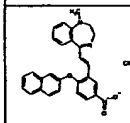
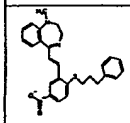
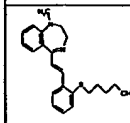
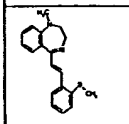
	Methyl (E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-yloxy]methyl]benzoate acetate (1:2)
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(4-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thienyl)-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(3-pyridyl)vinyl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-nitro-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-[3-(4-Chlorophenylthio)-5-(trifluoromethyl)-2-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2-(4-Chlorobenzylthio)-6-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-3-pyridinecarbonitrile dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-methoxy-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-6-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1H-1,4-benzodiazepine

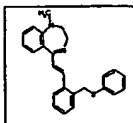
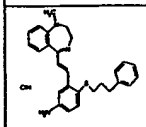
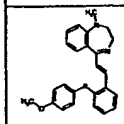
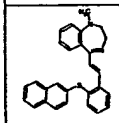
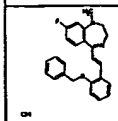
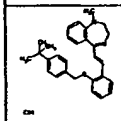
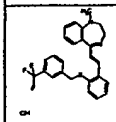
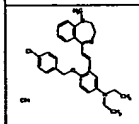
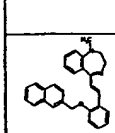
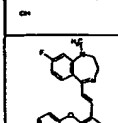
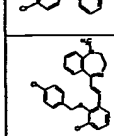
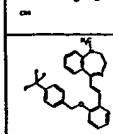
	(E)-2,3-Dihydro-1-methyl-5-[3-[(2-pyridyl)-methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(3-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(4-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-8-Bromo-5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(5-methyl-3-isoxazol-3-yl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-[(1-Benzyl-1H-imidazol-2-yl)methoxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-6-[2-(8-Bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-2-(4-chlorobenzylthio)-3-pyridinecarbonitrile dihydrochloride
	tert-Butyl (E)-2-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoate dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-8-bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-(4-methoxyphenyl)-1H-1,4-benzodiazepine hydrochloride

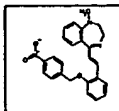
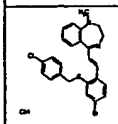
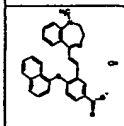
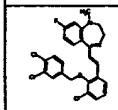
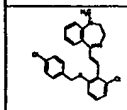
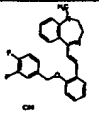
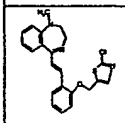
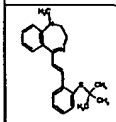
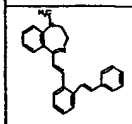
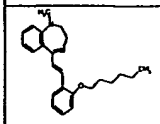
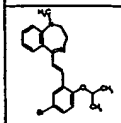
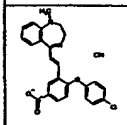
	Methyl (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate
	(E)-5-[4-(3-Bromophenyl)-3-pyridyl]-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2,3-Dihydro-3-(4-methoxybenzyloxy)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	Methyl (E)-4-[[3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenoxy]methyl]benzoate dihydrochloride
	(E)-4-[[5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(3,5-dimethyl-1-pyrazolyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-4'-[[3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenoxy]methyl]acetanilide hydrochloride
	(E)-4-Benzylthio-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoic acid acetate (1:1)
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(4-methoxybenzyl)benzamide hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxybenzyl)benzamide hydrochloride
	tert-Butyl (E)-[2-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)-vinyl]-benzamido]ethyl)]carbamate

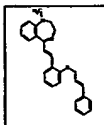
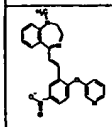
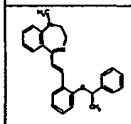
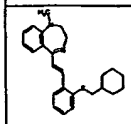
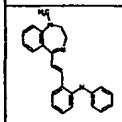
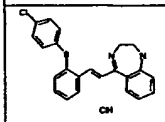
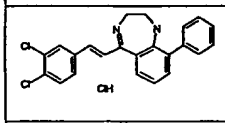
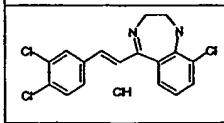
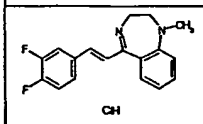
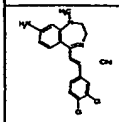
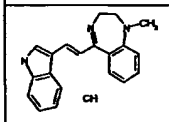
	Methyl (E)-4-[[5-(2-benzylthio-5-nitrostyryl)-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate
	(E)-2-Acetamido-4'-benzylthio-3'-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]acetanilide dihydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxybenzyl)benzamide hydrochloride
	(E)-N-(2-Aminoethyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-5-[2-[4-(4-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline hydrochloride
	(E)-N-[4-(Trifluoromethyl)benzyl]-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide
	tert-Butyl (E)-[3-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]propyl]carbamate
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(1H-indol-3-yl)ethyl]benzamide
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxyethyl)benzamide
	(E)-N-(3-Aminopropyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-methyl-4-nitroaniline dihydrochloride

	(E)-5-[2-(4-Chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthiostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	tert-Butyl (E)-(4-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]butyl)carbamate
	(E)-N-(4-Aminobutyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	tert-Butyl (E)-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]acetate
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(4-sulfamoylphenyl)ethyl]benzamide
	(E)-2,3-Dihydro-1-methyl-5-[2-(2-phenylethyl)styryl]-1H-1,4-benzodiazepine
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxypropyl)benzamide
	(E)-2,3-Dihydro-1-methyl-5-(5-nitro-2-phenoxystyryl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(4-methylbenzylthio)-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-5-[2-(4-methoxybenzylthio)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride

	(E)-5-(2-Benzylthio-5-nitrostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-4'-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenylthio]acetanilide hydrochloride
	(E)-5-(2-Fluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzyloxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenoxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(2-p-tolylthiostyryl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(3,4-Dichlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorobenzyloxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-phenylpropylthio)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-(2-pentylthiostyryl)-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-(2-methylthiostyryl)-1H-1,4-benzodiazepine

	(E)-2,3-Dihydro-1-methyl-5-[2-(phenylthiomethyl)-styryl]-1H-1,4-benzodiazepine
	(E)-3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-4-(3-phenylpropylthio)aniline hydrochloride
	(E)-2,3-Dihydro-5-[2-(4-methoxyphenylthio)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthylthio)styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthiostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-tert-Butyl-benzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[3-(Trifluoromethyl)benzylthio]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-4-(4-Chlorobenzyloxy)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N,N-diethylaniline dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-[(2-naphthyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenoxy)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-Chloro-2-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[4-(Trifluoromethyl)benzyloxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

	(E)-2,3-Dihydro-1-methyl-5-[2-(4-nitrobenzyloxy)styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[4-Bromo-2-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(1-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-Chloro-2-(3,4-dichlorobenzylthio)phenyl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-Chloro-6-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-(3,4-Difluorobenzyloxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[(2-Chloro-5-thiazolyl)methoxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-[2-(tert-Butylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(all-E)-2,3-Dihydro-1-methyl-5-(2-styrylstyryl)-1H-1,4-benzodiazepine
	(E)-5-(2-Hexyloxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(5-Bromo-2-isopropoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-[2-(4-Chlorophenoxy)-5-nitrostyryl]-3,4-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride

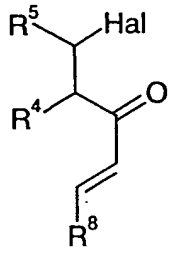
	(all-E)-2,3-Dihydro-1-methyl-5-[2-(styrylthio)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-pyridyloxy)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[2-(1(RS)-phenylethylthio)styryl]-1H-1,4-benzodiazepine
	(E)-5-[2-(Cyclohexylmethylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-N-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenyl]aniline
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-phenyl-1H-1,4-benzodiazepine hydrochloride
	(E)-9-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Difluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-amine hydrochloride
	(E)-2,3-Dihydro-5-[2-(1H-indol-3-yl)vinyl]-1-methyl-1H-1,4-benzodiazepine hydrochloride

The benzodiazepines provided by the present invention are potent inhibitors of the ATPase activity of the human papillomavirus E1 helicase enzyme. They accordingly are therapeutically active substances in the treatment of HPV mediated diseases

and therefore can be used as medicaments, either alone or combined with other therapeutically active agents.

The benzodiazepines provided by the present invention are in particular useful in combating HPV disease states such as cutaneous warts on any part of the body, including palmar, plantar and flat/plane warts, anogenital warts (condylomata acuminata), including external and internal (intraurethral, vaginal and cervical) warts, all grades of CIN (cervical intraepithelial neoplasia) and SIL (squamous intraepithelial lesions), recurrent laryngeal papillomatosis (laryngeal warts), epidermodysplasia verruciformis, focal epithelial hyperplasia (Heck's disease), warts or intraepithelial neoplasia affecting the oral and nasal cavities and conjunctival warts.

The compounds of the present invention can be prepared by coupling of a compound of formula



IV

wherein R^4 and R^5 are as above and Hal is a halogen atom with a diamine of formula

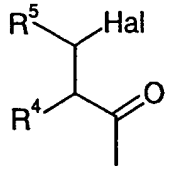
$$R^1NH(CH_2CH_2)NH_2 \qquad V$$

wherein R^1 is as above.

The reaction can be carried out in a conventional manner known to the skilled in the art or following the adaption of a method provided in . Journal of Organic Chemistry (1963) p 3013 by Sternbach et al, suitably in .pyridine as solvent and at elevated temperature.

The compounds of formula IV and V are new intermediates not known to the state of the art and therefore are also subject of the present invention.

The compounds of formula IV are accessible by condensation of a ketone of formula



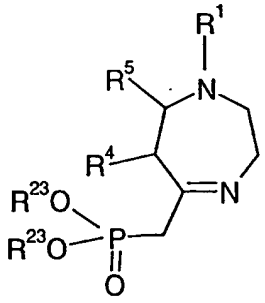
VI

wherein R^4 and R^5 are as above and Hal is a halogen atom
with an aldehyde of the formula

R^8CHO VII

wherein R^8 is as above following methods known to the skilled in the art.

Alternatively the compounds of the present invention can be prepared by coupling of a phosphoric acid ester of formula



VIII

wherein R^1, R^4 and R^5 are as above and wherein R^{23} is lower alkyl
with an aldehyde of the formula

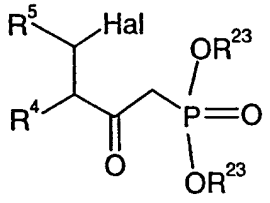
R^8CHO VII

wherein R^8 is as above.

The reaction can be carried out in a conventional manner known to the skilled in the art or following the adaption of a method provided in Buzas and Finet,

Tetrahedron Letters 1976, p 2433, suitably in the presence of an alkali metal hydride in tetrahydrofuran.

The phosphoric acid ester of formula VIII is accessible by a reaction of a compound of formula



IX

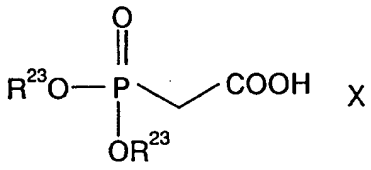
wherein R^4, R^5 and R^{23} and Hal are as above with a diamine of the formula

$$R^1NH(CH_2CH_2)NH_2 \qquad V$$

wherein R^1 is as above.

The intermediates of formulas VII, VIII, IX and X are not known to the state of the art and are therefore also subject of the present invention.

The compound of formula IX itself can be synthesized starting from a ketone of formula VI by a conversion with a compound of formula



X

wherein R^{23} is as above. This process can be carried out using methods known to the skilled in the art following the adaption of a method provided in Kim et al, Journal of the Chemical Society, Perkin Transactions I 1997, pp 1361 .

With regard to the starting materials that are known compounds some of these may be purchased from commercial suppliers. Other starting materials that are known and their analogues can be prepared by methods well known in the art.

For assaying E1 ATPase activity the HPV E1 enzyme has been prepared and purified as follows:

The HPV(11) E1 used in this assay is expressed as a maltose binding protein (MBP) fusion protein from SF9 cells using a baculovirus expression system. Frozen pellets of these cells are thawed by adding the pellet directly into a buffer at 4 OC containing 50mM Tris-HCl pH 7.5, 20mM dithiothreitol (DTT), 1mM EDTA, 600mM NaCl, 20% glycerol and 3 "Complete" protease inhibitor tablets/50ml (Boehringer Mannheim cat.no.1 697 498). The cell suspension is then sonicated for 3x10 seconds before centrifuging at 18 000 rpm for 30 minutes to remove the cell debris. The clarified extract is then passed down a DE52 ion exchange column which is washed with a buffer containing 50mM Tris-HCl pH 7.5, 2mM DTT, 1mM EDTA, 600mM NaCl and 20% glycerol. The column flow through plus the first 10 mls of wash buffer are then passed down an amylose affinity column which binds MBP tagged proteins. This column is washed with 3 column bed volumes of the wash buffer before being eluted with wash buffer containing 10mM maltose. The eluted protein peak containing purified HPV(11) E1 is then dialysed overnight against 2L of buffer containing 20mM Tris-HCl pH 7.5, 2mM DTT, 20mM NaCl and 20% glycerol. The dialyzed material is used in the assay.

E1 ATPase activity can be measured as follows:

The standard reaction contains 50mM MOPs KOH pH 7.0, 500µM MgCl2, 20µM ATP, 50mM NaCl , 40µl of a suitably diluted enzyme extract and 10µl of inhibitor in a final volume of 100µl. The ATP contains 0.1µCi [γ^{33}P]ATP per reaction. The enzyme diluent contains 50mM MOPs KOH pH7.0 and 1mg/ml BSA. The inhibitor is diluted to give a range of concentrations in neat DMSO. Reaction tubes are incubated for 1 hour at 37°C (producing linear kinetics) after which the reaction is terminated by heat inactivation at 85°C for 2 minutes. 500µl 15% activated charcoal in PBS is then added to each reaction. The activated charcoal used is 100 - 400 mesh untreated powder (Sigma cat No C-5260); prior to use in the assay this is washed in PBS several times and allowed to settle out under gravity, any fine particles still in suspension being decanted off after each wash. The reactions are left on ice for 1 hour after which the charcoal is pelleted out by centrifugation at 14 000 rpm for 10 minutes. The charcoal pellet contains unconverted [γ^{33}P]ATP, whilst any free inorganic ^{33}P, the reaction product, will

remain in the supernatant. The amount of radioactivity present in 300µl of supernatant is then measured by scintillation spectrophotometry.

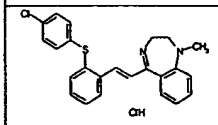
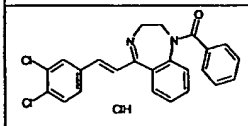
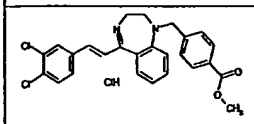
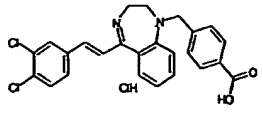
The results can be calculated as follows:

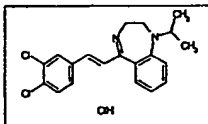
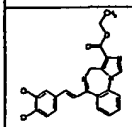
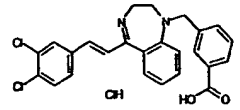
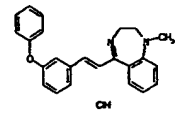
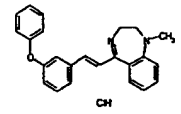
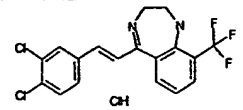
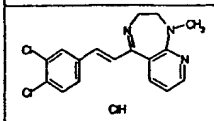
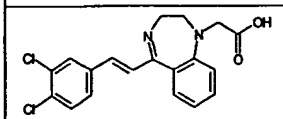
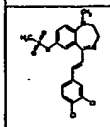
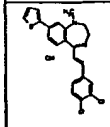
The degree of inhibition at each inhibitor concentration is expressed as a percentage of the control reaction (100%) after subtracting a measured blank value, which represents the amount of free inorganic ^{33}P present in a reaction containing heat inactivated enzyme. An IC_{50} value (concentration of test compound which inhibits enzyme activity by 50%) is then calculated from a dose response curve of $\log_{10}$ inhibitor concentration against percentage of the control reaction.

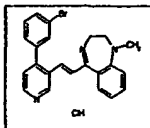
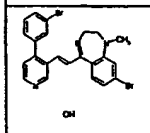
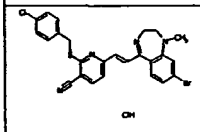
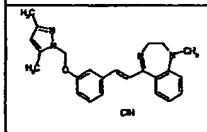
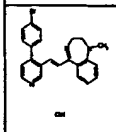
Preferred compounds of the invention tested in the above assay have an IC_{50} value up to about 50 µM.

Specific examples of IC_{50} values for some compounds of the invention are set out in the table B below.

Table B

Structure	Activity/µM	Example No.
	1.6	121
	5.6	125
	2.2	127
	4.4	132

	2	123
	20	139
	3.1	133
	2.4	3
	26	136
	5.6	38
	3	29
	20	137
	8.6	162
	12	164

	4.2	6
	2.4	42
	2.5	44
	19	92
	5.4	147

The compound of the present invention as well as its pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions or topically, e.g. in the form of a cream, a gel or a solution.

The compound of the present invention and its pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Suitable excipients for topical gels are e.g. natural gums such as xanthan and tragacanth, semisynthetic cellulose derivatives such as methylcelluloses and carboxymethylcelluloses, carbomers, clays such as silicates and presevatives such as benzoic acid or parabens.

Suitable excipients for topical creams are e.g oils and waxes, emulsifying agents such as surfactants and polymers such as polyoxamers and preservatives.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of the compound of formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following examples illustrate the present invention:

Example 1

(E)-5-(3,4-Difluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To a solution of 43 mg (0.14 mmol) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2.5 ml of tetrahydrofuran was added 8.3 mg (0.21 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 19.9 mg (0.14 mmol) of 3,4-

difluorobenzaldehyde was added and the mixture was stirred for 2.75 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 3% methanol/ethyl acetate and treated with 0.05 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave a red gum which was recrystallized from ethyl acetate – petroleum ether (40 - 60°C) to give 14 mg of (E)-5-(3,4-difluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as dark red crystals. 1H NMR (400 MHz, DMSO) δ: 2.97 (s, 3H), 3.77 (m, 2H), 3.83 (m, 2H), 7.06 (t, 1H), 7.18 (d, 1H), 7.50 (2H, dd), 7.55-7.70 (m, 4H), 7.95 (m, 1H); MS: m/e 298 (M+).

The starting material was prepared as follows:

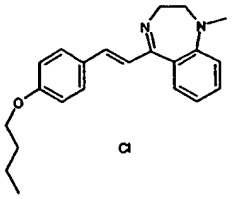
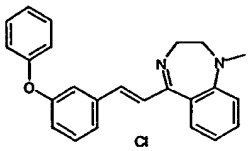
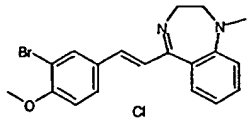
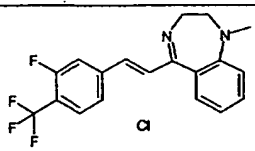
i) To a solution of 2.34 g (11.9 mmol) of diethylphosphonoacetic acid in toluene at 0°C was added 4.82 g (47.7 mmol) of triethylamine followed by 1.94 g (17.9 mmol) of chlorotrimethylsilane. The mixture was stirred at ambient temperature for 1 hour, then 1.13 g (11.9 mmol) of magnesium chloride was added and the mixture was stirred for a further 1 hour. To the mixture was added 2.0 g (14.3 mmol) of 2-fluorobenzoyl chloride and the mixture was stirred for 72 hours. The mixture was partitioned between 200 ml of water and 250 ml, 100 ml of dichloromethane. The combined organic portions were dried (magnesium sulphate), filtered and evaporated . The residue was purified by column chromatography eluting with 3 – 5% methanol/dichloromethane to give 2.1 g (64%) of [2-(2-fluorophenyl)-2-oxoethyl]phosphonic acid diethyl ester as a colourless oil; MS: m/e 274.9 $[M+H]^+$.

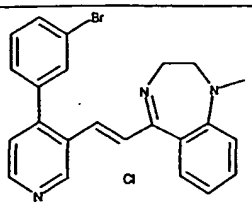
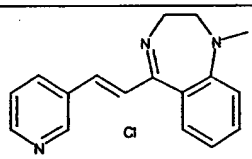
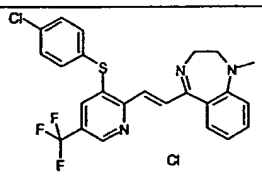
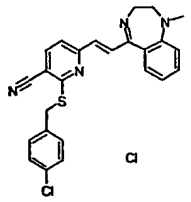
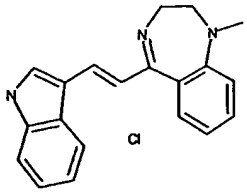
ii) A mixture of 10.45 g (38.1 mmol) of [2-(2-fluorophenyl)-2-oxoethyl]phosphonic acid diethyl ester and 14.1 g (190 mmol) N-methylethylenediamine in 100 ml of pyridine was heated at 95°C for 18 hours. The solvent was evaporated and the residue was partitioned between 200 ml of water and 2 x 100 ml of dichloromethane. The combined organic portions were dried (magnesium sulphate), filtered and evaporated. The residue was purified by column chromatography eluting with 5% methanol/dichloromethane to give 3.14 g (26%) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester as a light brown oil; MS: m/e 311.0 $[M+H]^+$.

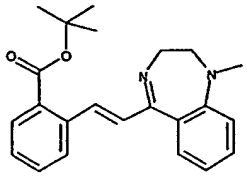
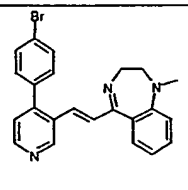
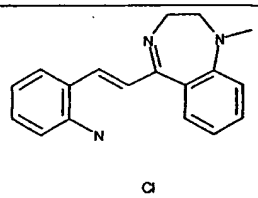
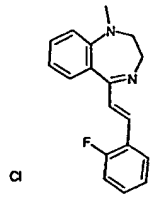
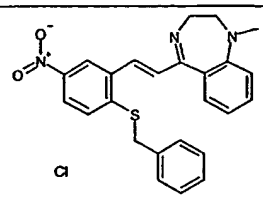
In a manner analogous to that described in Example 1, starting with (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl

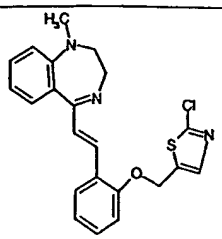
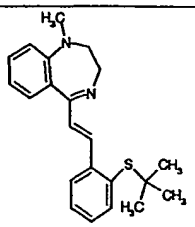
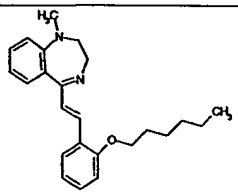
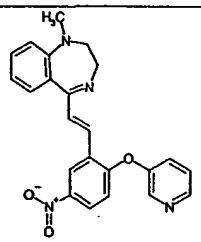
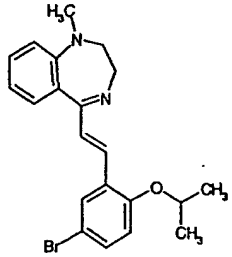
ester (prepared as described in Example 1), and the appropriate aldehyde, the compounds shown in Table 1 were also prepared:

Table 1

Compound	Structure	Name	MS (ES) (M+H)+
Example 2		(E)-5-(4-Butoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	334 (M^+; EI)
Example 3		(E)-2,3-Dihydro-1-methyl-5-(3-phenoxystyryl)-1H-1,4-benzodiazepine dihydrochloride	354 (M^+; EI)
Example 4		(E)-5-(3-Bromo-4-methoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	370 (M^+; EI)
Example 5		(E)-5-[3-Fluoro-4-(trifluoromethyl)styryl]-2,3-dihydro-1-methyl-1H-benzo[e][1,4]diazepine dihydrochloride	348 (M^+; EI)

Example 6		(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	416 (M^+; EI)
Example 7		(E)-2,3-Dihydro-1-methyl-5-[2-(3-pyridyl)vinyl]-1H-1,4-benzodiazepine dihydrochloride	263 (M^+; EI)
Example 8		(E)-5-[2-[3-(4-Chlorophenylthio)-5-(trifluoromethyl)-2-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	473 (M^+; EI)
Example 9		(E)-2-(4-Chlorobenzylthio)-6-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-3-pyridinecarbonitrile dihydrochloride	445 (M^+)
Example 10		(E)-2,3-Dihydro-5-[2-(1H-indol-3-yl)vinyl]-1-methyl-1H-1,4-benzodiazepine	302 (M^+)

		dihydrochloride	
Example 11		tert-Butyl (E)-2-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoate dihydrochloride	362 (M^+; EI)
Example 12		(E)-5-[2-[4-(4-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	418 (M^+; EI)
Example 13		(E)-2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline dihydrochloride	277 (M^+; EI)
Example 14		(E)-5-(2-Fluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	280 (M^+; EI)
Example 15		(E)-5-(2-Benzylthio-5-nitrostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	429 (M^+; EI)

Example 16		(E)-5-[2-[(2-Chloro-5-thiazolyl)methoxy] styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine	410.2
Example 17		(E)-5-[2-(tert-Butylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine	351.3
Example 18		(E)-5-(2-Hexyloxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine	363.4
Example 19		(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-pyridyloxy)styryl]-1H-1,4-benzodiazepine	401.2
Example 20		(E)-5-(5-Bromo-2-isopropoxy-styryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine	399.2

Example 21

(E)-2,3-Dihydro-1-methyl-5-[2-(2-phenylethyl)styryl]-1H-1,4-benzodiazepine

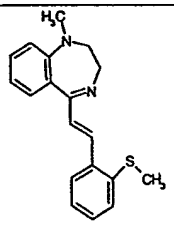
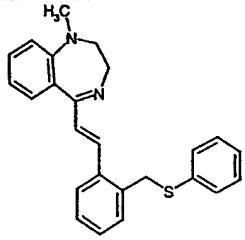
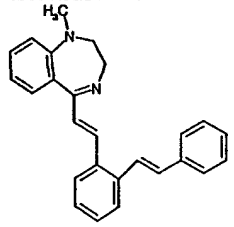
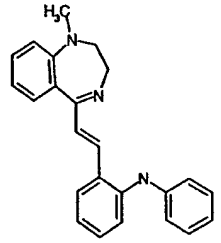
In an analogous fashion to Example 1 was prepared (E)-2,3-dihydro-1-methyl-5-[2-(2-phenylethyl)styryl]-1H-1,4-benzodiazepine as a light yellow oil, MS: m/e 367.3 $[M+H]^+$.

The aldehyde starting material was prepared as follows:

A mixture of 3g (13.2 mmol) of 2-phenethylbenzoic acid, 3.8g (19.8 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 2.7 g (20.0 mmol) of 1-hydroxybenzotriazole hydrate, 3 ml (23 mmol) of N-ethylmorpholine and 1.94 g (19.9 mmol) of N,O-dimethylhydroxylamine hydrochloride was stirred in 50 ml of dichloromethane at room temperature for 2 hours. The solution was diluted with dichloromethane and washed sequentially with saturated aqueous citric acid solution and saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to afford N-methoxy-N-methyl-2-phenethylbenzamide as a colourless oil. To a solution of 1g (3.7 mmol) of this oil in 10 ml tetrahydrofuran at 0°C was added 2.2 ml of a 1M solution of lithium aluminium hydride in tetrahydrofuran. The solution was stirred at 0°C for 25 minutes and saturated aqueous potassium hydrogensulphate and ether were then added and the mixture stirred at room temperature for 30 minutes. The layers were separated and the organic layer washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to afford 2-phenethyl-benzaldehyde as a colourless oil which was used directly without further purification.

In an analogous fashion to Example 21, by replacing 2-phenethylbenzoic acid with the appropriate carboxylic acid, the compounds shown in Table 2 were also prepared:

Table 2

Compound	Structure	Name	MS (ES) (M+H)+
Example 22		(E)-2,3-Dihydro-1-methyl-5-(2-methylthiostyryl)-1H-1,4-benzodiazepine	309.2
Example 23		(E)-2,3-Dihydro-1-methyl-5-[2-(phenylthiomethyl)styryl]-1H-1,4-benzodiazepine	385.3
Example 24		(E,E)-2,3-Dihydro-1-methyl-5-(2-styrylstyryl)-1H-1,4-benzodiazepine	365.3
Example 25		(E)-N-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzo-diazepin-5-yl)vinyl]phenyl]aniline	354.3

Example 26

(E,E)-2,3-Dihydro-1-methyl-5-[2-(styrylthio)styryl]-1H-1,4-benzodiazepine

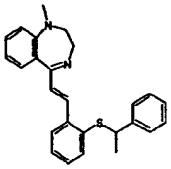
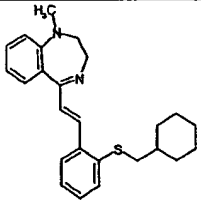
In an analogous fashion to Example 21 there was obtained (E,E)-2,3-Dihydro-1-methyl-5-[2-(styrylthio)styryl]-1H-1,4-benzodiazepine as a yellow gum, MS (ES) $(M+H)^+$ 411.2.

The carboxylic acid starting material was prepared as follows:

To a solution of 1.28 g (6.49 mmol) of cinnamyl bromide in 8 ml of ethanol at room temperature under an atmosphere of nitrogen was added a solution of 1g (6.49 mmol) of thiosalicylic acid in 5.3 ml of 10% aqueous sodium hydroxide solution. The solution was stirred at room temperature for 16 hours and the solvent then removed under reduced pressure. The residue was dissolved in water and concentrated hydrochloric acid was added. The resultant solid was filtered off and dried. There was obtained 1.7 g of 2-styrylsulfanylbenzoic acid as a white solid, MS: m/e 270 M^+.

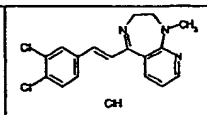
In an analogous fashion to Example 26, by replacing cinnamyl bromide with the appropriate bromide the compounds shown in Table 3 were also prepared:

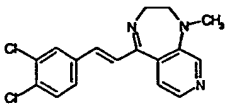
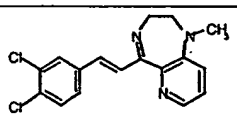
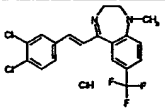
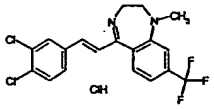
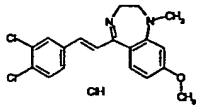
Table 3

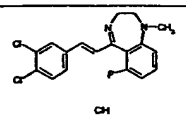
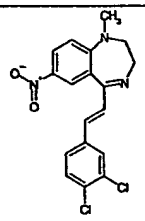
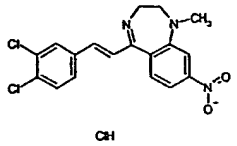
Compound	Structure	Name	MS (ES) (M+H)+
Example 27		(E)-2,3-Dihydro-1-methyl-5-[2-(1(RS)-phenylethylthio)styryl]-1H-1,4-benzodiazepine	399.3
Example 28		(E)-5-[2-(Cyclohexylmethylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine	391.3

In an analogous fashion to Example 1, using the appropriate acid chloride, and 3,4 dichlorobenzaldehyde the compounds shown in Table 4 were also prepared:

Table 4

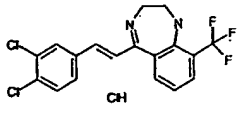
Example 29		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-	332.1

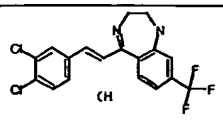
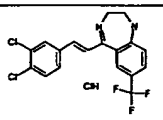
		1H-pyrido[2,3-e][1,4]diazepine hydrochloride (1:3)	
Example 30		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,4-e][1,4]diazepine	332.1
Example 31		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,2-e][1,4]diazepine	332.2
Example 32		(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride	399.1
Example 33		(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride	398.8
Example 34		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-methoxy-1-methyl-1H-1,4-benzodiazepine hydrochloride	361.2

Example 35		(E)-5-(3,4-Dichlorostyryl)-6-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride	349.2
Example 36		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-7-nitro-1H-1,4-benzodiazepine	376.1
Example 37		(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-nitro-1H-1,4-benzodiazepine hydrochloride	376.2

In an analogous fashion to Example 1, replacing 3,4-difluorobenzaldehyde with 3,4 dichlorobenzaldehyde, and N-methylethylenediamine with ethylenediamine, and using the appropriate acid chloride, the compounds shown in Table 5 were also prepared:

Table 5

Example 38		(E)-5-(3,4-Dichlorostyryl)-9-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride	385.5

Example 39		(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride	385.1
Example 40		(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride	384.8

Example 41

(E)-8-Bromo-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

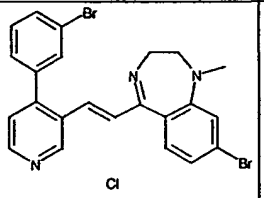
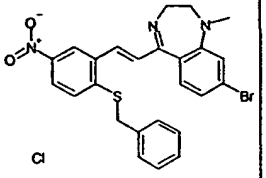
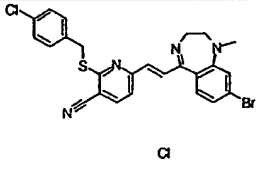
To 122 mg (0.31 mmol) of (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2.5 ml of tetrahydrofuran was added 26 mg (0.55 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 57 mg (0.33 mmol) of 3,4-difluorobenzaldehyde was added and the mixture was stirred for 6 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/dichloromethane and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave a red gum which was recrystallized from acetone – petroleum ether (40 - 60°C) to give 77 mg of (E)-5-(3,4-difluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as orange crystals; MS: m/e 408 (M^+).

The starting material was prepared as follows:

(8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester was prepared in an analogous fashion to (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester, prepared in Example 1, by replacing 2-fluorobenzoic acid with 2-fluoro-4-bromobenzoic acid.

In a manner analogous to that described in Example 41, starting with (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 41), and the appropriate aldehyde, the compounds shown in Table 6 were also prepared:

Table 6

Compound	Structure	Name	MS (ES) (M+H)+
Example 42		(E)-8-Bromo-5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	429 (M^+; EI)
Example 43		(E)-5-(2-Benzylthio-5-nitrostyryl)-8-bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	507 (M^+; EI)
Example 44		(E)-6-[2-(8-Bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-2-(4-chlorobenzylthio)-3-pyridinecarbonitrile dihydrochloride	523 ($[M+H]^+$; EI)

Example 45

(E)-9-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride

To a solution of 91 mg (0.275 mmol) of (9-chloro-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2 ml of tetrahydrofuran was added 19 mg (0.48 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 50 mg (0.29 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 18 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/dichloromethane and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to give 90 mg of (E)-9-chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: m/e 352.7 $[M+H]^+$.

The starting material was prepared as follows:

(9-chloro-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester was prepared in an analogous fashion to (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester, prepared in Example 1, by replacing 2-fluorobenzoic acid with 2-fluoro-3-chlorobenzoic acid and N-methylethylenediamine with ethylenediamine.

Example 46

(E)-5-[4-(3-Bromophenyl)-3-pyridyl]-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To 95 mg (0.289 mmol) of (7-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2 ml of tetrahydrofuran was added 20 mg (0.51 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 80 mg (0.30 mmol) of 3-formyl-4-(3-bromophenyl)pyridine was added and the mixture was stirred for 18 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/dichloromethane and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was triturated with diethyl ether to give 10 mg of (E)-5-[4-(3-bromophenyl)-3-pyridyl]-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as a dark red solid; MS: m/e 437.8 $[M+H]^+$.

The starting material was prepared as follows:

(7-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester was prepared in an analogous fashion to (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester, prepared in Example 1, by replacing 2-fluorobenzoic acid with 2,5-difluorobenzoic acid.

Example 47

(E)-5-(2-Benzylthio-5-nitrostyryl)-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

In a manner analogous to that described in Example 46, starting with (7-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 46), and 2-benzylthio-5-nitrobenzaldehyde there was obtained (E)-5-(2-benzylthio-5-nitrostyryl)-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride, MS: m/e 448 $[M+H]^+$.

Example 48

(E)-8-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

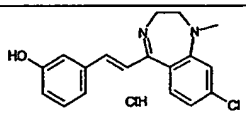
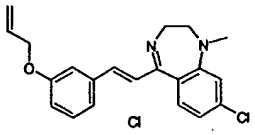
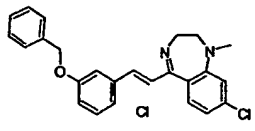
To 210 mg (0.609 mmol) of (8-chloro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 4 ml of tetrahydrofuran was added 36 mg (0.91 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 112 mg (0.64 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 18 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 2% methanol/dichloromethane and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallised from acetone – petroleum ether (40-60°C) to give 40 mg of (E)-9-chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride as yellow needles; MS: m/e 364 (M^+).

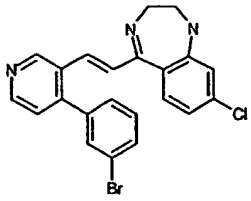
The starting material was prepared as follows:

(8-chloro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester was prepared in an analogous fashion to (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)-phosphonic acid diethyl ester, as described in Example 1 by replacing 2-fluorobenzoic acid with 4-chloro-2-fluorobenzoic acid.

In a manner analogous to that described in Example 48, starting with (8-chloro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 48), and the appropriate aldehyde the compounds shown in Table 7 were also prepared:

Table 7

Compound	Structure	Name	MS (ES) (M+H)+
Example 49		(E)-3-[2-(8-Chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenol dihydrochloride	312
Example 50		(E)-5-(3-Allyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	352 (M^+; EI)
Example 51		(E)-5-(3-Benzyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	402 (M^+; EI)

Example 52		(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1H-1,4-benzodiazepine	440.2

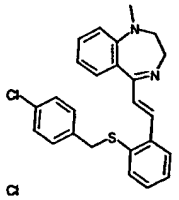
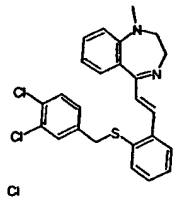
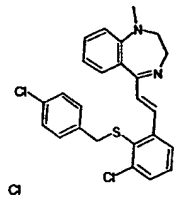
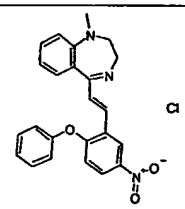
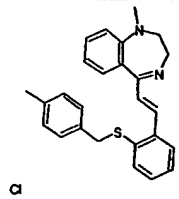
Example 53

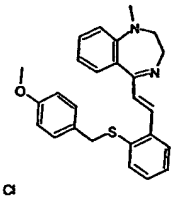
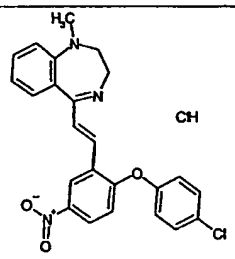
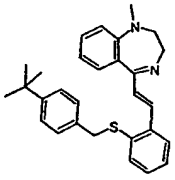
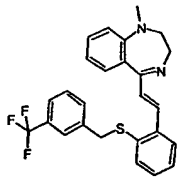
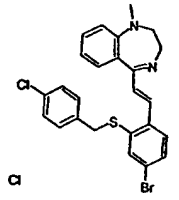
(E)-5-(2-Benzylthiostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

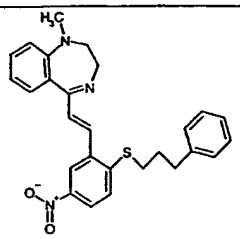
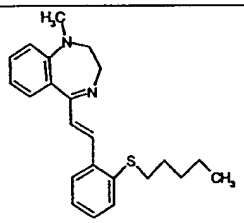
To a mixture of 56 mg of 2-fluorobenzaldehyde (0.45 mmol) and 56 mg (0.45 mmol) of benzyl mercaptan in 3 ml of tetrahydrofuran was added 22 mg of sodium hydride (60% dispersion in mineral oil). After 1.2 hours 112 mg (0.36 mmol) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1) was added followed by 25 mg (0.63 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred for 1.3 hours. The mixture was partitioned between 20 ml of water and 5 ml of dichloromethane. The organic portion was dried (magnesium sulphate), filtered and evaporated.The product was purified by column chromatography (20 g IST pre-packed column) eluting with 0 - 2% methanol/dichloromethane and treated with 0.25 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave a red gum which was lyophilised to give 75 mg of (E)-5-(2-benzylthiostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as dark red powder; MS: m/e 385 $[M+H]^+$.

In a manner analogous to that described in Example 1, starting with (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1), and the appropriate aldehyde, prepared in a similar fashion to that for Example 53, the compounds shown in Table 8 were also prepared:

Table 8

Compound	Structure	Name	MS (ES) (M+H)+
Example 54		(E)-5-[2-(4-Chlorobenzylthio)-styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	418.9
Example 55		(E)-5-[2-(3,4-Dichlorobenzylthio)-styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	452 (M^+; EI)
Example 56		5-[3-Chloro-2-(4-chlorobenzylthio)-styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	453 (M^+)
Example 57		(E)-2,3-Dihydro-1-methyl-5-(5-nitro-2-phenoxystyryl)-1H-1,4-benzodiazepine dihydrochloride	399 (M^+; EI)
Example 58		(E)-2,3-Dihydro-1-methyl-5-[2-(4-methylbenzylthio)-styryl]-1H-1,4-benzodiazepine dihydrochloride	399

Example 59		(E)-2,3-Dihydro-5-[2-(4-methoxybenzyl-thio)styryl]-1-methyl-1H-1,4-benzo-diazepine dihydrochloride	415
Example 60		(E)-5-[2-(4-Chlorophenoxy)-5-nitrostyryl]-3,4-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride	434.2
Example 61		(E)-5-[2-(4-tert-Butyl-benzylthio)-styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	440 (M^+; EI)
Example 62		(E)-5-[2-[3-(Trifluoromethyl)benzylthio]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzo-diazepine dihydrochloride	452 (M^+; EI)
Example 63		(E)-5-[4-Bromo-2-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	496 (M^+; EI)

Example 64		(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-phenylpropylthio)-styryl]-1H-1,4-benzodiazepine	458.0
Example 65		(E)-2,3-Dihydro-1-methyl-5-(2-pentylthiostyryl)-1H-1,4-benzodiazepine	365.3

Example 66

(E)-5-[2-Chloro-6-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 53 by replacing 2-fluorobenzaldehyde by 2-chloro-6-nitrobenzaldehyde and benzyl mercaptan with 4-chlorobenzyl mercaptan there was obtained (E)-5-[2-chloro-6-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride MS: m/e 452 $[M+H]^+$.

Example 67

2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-methyl-4-nitroaniline dihydrochloride

To a solution of 145 mg (0.47 mmol) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1) in 3 ml of tetrahydrofuran was added 33 mg (0.82 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 133 mg (0.49 mmol) of 2-(benzylmethylamino)-5-nitrobenzaldehyde was added and the mixture was stirred for 0.7 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 2% methanol/dichloromethane and treated with 0.25 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave 228 mg of 2-[2-(2,3-dihydro-1-

methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-methyl-4-nitroaniline dihydrochloride as an orange solid; MS: m/e 427 $[M+H]^+$.

The starting material was prepared as follows:

A mixture of 300 mg (1.62 mmol) of 2-chloro-5-nitrobenzaldehyde, 196 mg (1.62 mmol) of N-benzylmethylamine and 268 mg (1.94 mmol) of potassium carbonate in dimethylformamide was heated at 80°C for 5 hour. The solvent was removed and the residue was partitioned between water and ethyl acetate (x2). The combined organic phases were evaporated and the residue was purified by column chromatography eluting with 25% ethyl acetate/petroleum ether (40-60°C) to give 290 mg of 2-(benzylmethylamino)-5-nitrobenzaldehyde as a yellow oil which solidified on standing; MS: m/e 270.9 $[M+H]^+$.

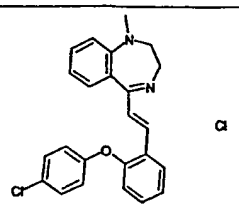
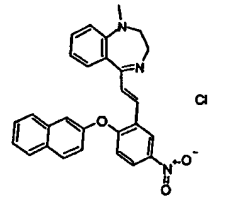
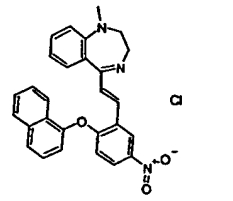
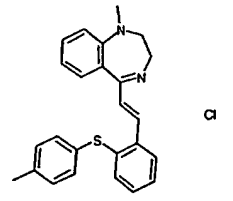
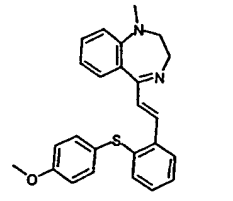
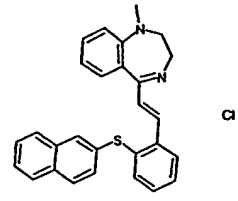
Example 68

(E)-4'-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenylthio]acetanilide dihydrochloride

To a mixture of 56 mg of 2-fluorobenzaldehyde (0.45 mmol) and 75 mg (0.45 mmol) of 4-acetamidothiophenol in 2.5 ml of dimethylformamide was added 62 mg of potassium carbonate. The mixture was heated at 65°C for 0.75 hours then allowed to cool. To the mixture was added 112 mg (0.36 mmol) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1) was added followed by 25 mg (0.63 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred for 1 hour. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1 - 6% methanol/ethyl acetate and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave 20 mg of a red gum which was recrystallised from methanol/acetone/petroleum ether (40-60°C) to give 2 mg of (E)-4'-[2-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenylthio]acetanilide dihydrochloride as dark red powder; MS: m/e 428 $[M+H]^+$.

In a manner analogous to that described in Example 1, starting with (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1), and the appropriate aldehyde, prepared in a similar fashion to that for Example 68, the compounds shown in Table 9 were also prepared:

Table 9

Example 69		(E)-5-[2-(4-Chlorophenoxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	388 (M^+; EI)
Example 70		(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride	449 (M^+; EI)
Example 71		(E)-2,3-Dihydro-1-methyl-5-[2-(1-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride	450 (M^+)
Example 72		(E)-2,3-Dihydro-1-methyl-5-(2-p-tolylthiostyryl)-1H-1,4-benzodiazepine dihydrochloride	385
Example 73		(E)-2,3-Dihydro-5-[2-(4-methoxyphenyl-thio)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride	400 (M^+; EI)
Example 74		(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthylthio)styryl]-1H-1,4-benzodiazepine dihydrochloride	420 (M^+; EI)

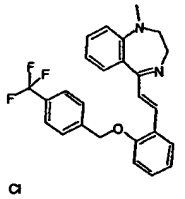
Example 75

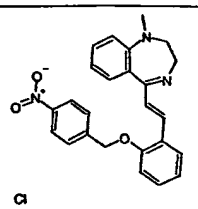
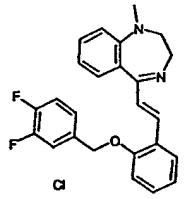
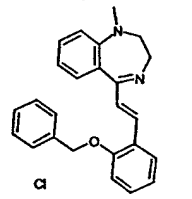
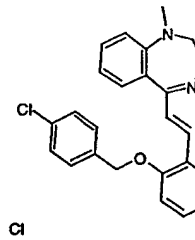
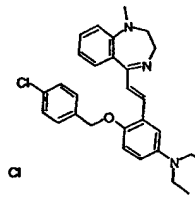
(E)-2,3-Dihydro-1-methyl-5-[2-[(2-naphthyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride

To a mixture of 55 mg (0.45 mmol) of 2-hydroxybenzaldehyde and 99 mg (0.45 mmol) of 2-bromomethylnaphthalene in 3 ml of tetrahydrofuran was added 124 mg (0.90 mmol) of potassium carbonate. The mixture was heated at 65°C for 18 hours before 112 mg (0.36 mmol) of (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1) was added followed by 25 mg (0.63 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred for 18 hours. The mixture was purified by column chromatography (20 g IST pre-packed column) eluting with 2% methanol/ethyl acetate and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallised from methanol/ethyl acetate/ether to give 63 mg of (E)-2,3-dihydro-1-methyl-5-[2-[(2-naphthyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: e/z 419 $[M+S]^+$.

In a manner analogous to that described in Example 75, starting with (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 1), and the appropriate aldehyde, prepared in a similar fashion to that for Example 75, the compounds shown in Table 10 were also prepared:

Table 10

Compound	Structure	Name	MS (ES) $(M+H)^+$
Example 76	 a	(E)-5-[2-[4-(Trifluoromethyl)benzyloxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	437

Example 77		(E)-2,3-Dihydro-1-methyl-5-[2-(4-nitrobenzyloxy)styryl]-1H-1,4-benzodiazepine dihydrochloride	413 (M^+; EI)
Example 78		(E)-5-[2-(3,4-Difluorobenzyloxy)-styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	334 (M^+; EI)
Example 79		(E)-5-(2-Benzyloxy-styryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	369
Example 80		(E)-5-[2-(4-Chloro-benzyloxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzo-diazepine dihydrochloride	402 (M^+; EI)
Example 81		(E)-4-(4-Chlorobenzyloxy)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N,N-diethylaniline dihydrochloride	474

Example 82

(E)-4-Benzylthio-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline dihydrochloride

To 215 mg (0.50 mmol) of (E)-5-(2-benzylthio-5-nitrostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride (prepared as described in Example 15) in 8 ml of tetrahydrofuran and 8 ml of ethanol was added 380 mg (0.90 mmol) of tin (II) chloride and 0.48 ml of concentrated hydrochloric acid. The mixture was heated at 60°C for 7 hours. The solution was reduced to half volume and partitioned between 50 ml of saturated sodium hydrogen carbonate solution and 100 ml and 50 ml of dichloromethane. The combined organic phases were dried (magnesium sulphate), filtered and evaporated. The residue was purified by column chromatography eluting with 2 - 5% methanol/dichloromethane and treated with 0.30 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallised from methanol/ether to give 46 mg of (E)-4-benzylthio-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline dihydrochloride as dark red crystals; MS: m/e 400 $[M+H]^+$.

Example 83

(E)-3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-4-(3-phenylpropylthio)aniline hydrochloride

In an analogous fashion to Example 82 from (E)-2,3-dihydro-1-methyl-5-[5-nitro-2-(3-phenylpropylthio)styryl]-1H-1,4-benzodiazepine (prepared as described in Example 75)there was obtained (E)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-4-(3-phenylpropylthio)aniline hydrochloride as a dark red solid MS: m/e 428.0 $[M+H]^+$.

Example 84

(E)-2-Acetamido-4'-benzylthio-3'-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]acetanilide dihydrochloride

To a mixture of 58 mg (0.114 mmol) of (E)-4-benzylthio-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline dihydrochloride (prepared as described in Example 82), 20 mg (0.171 mmol) of N-acetylglycine and 1-hydroxy-7-azabenzotriazole in 5 ml of dimethylformamide was added 44 mg (0.228 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The mixture

was stirred for 4 hours. The solvent was removed and the residue was purified by column chromatography eluting with 5 - 20% methanol/dichloromethane and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallised from acetone/methanol/diethyl ether to give 10 mg of (E)-2-acetamido-4'-benzylthio-3'-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]acetanilide dihydrochloride as a yellow solid; MS: m/e 499 (M^+).

Example 85

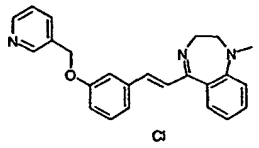
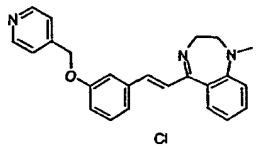
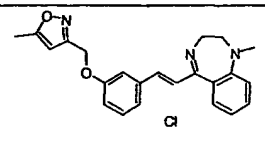
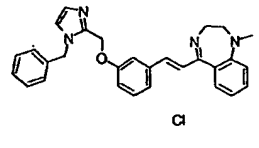
(E)-2,3-Dihydro-1-methyl-5-[3-[(2-pyridyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride

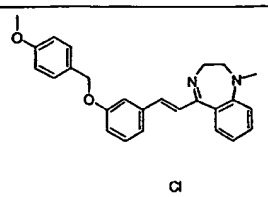
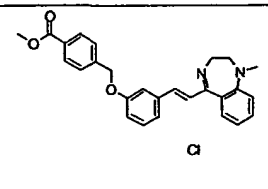
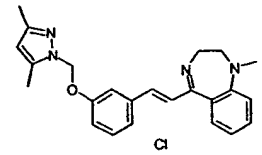
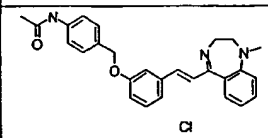
To a mixture of 74 mg (0.266 mmol) of (E)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenol and 29 mg (0.266 mmol) of 2-pyridylmethanol in 4 ml of tetrahydrofuran was added 134 mg (0.40 mmol) of polymer supported triphenylphosphine followed by 91 mg (0.40 mmol) of di-tert-butylazodicarboxylate. After 19 hours a further 134 mg (0.40 mmol) of polymer supported triphenylphosphine was added and the mixture was stirred for 72 hours. The mixture was filtered and the product was purified by column chromatography (20 g IST pre-packed column) eluting with 5% methanol/ethyl acetate and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue lyophilised to give 26 mg of (E)-2,3-dihydro-1-methyl-5-[3-[(2-pyridyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride as a dark red solid; MS: m/e 370 $[M+H]^+$.

The starting material, (E)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenol was prepared in an analogous fashion to Example 1, replacing 3,4-difluorobenzaldehyde by 2-hydroxybenzaldehyde.

In a manner analogous to that described in Example 85, starting with (E)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenol and the appropriate alcohol, the compounds shown in Table 11 were also prepared:

Table 11

Compound	Structure	Name	MS (ES) $(M+H)^+$
Example 86		(E)-2,3-Dihydro-1-methyl-5-[3-[(3-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride	370
Example 87		(E)-2,3-Dihydro-1-methyl-5-[3-[(4-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride	370
Example 88		(E)-2,3-Dihydro-1-methyl-5-[3-[(5-methyl-3-isoxazolyl)-methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride	374
Example 89		(E)-5-[3-[(1-Benzyl-1H-imidazol-2-yl)methoxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride	448 $(M^+; EI)$

Example 90		(E)-5-[2,3-Dihydro-3-(4-methoxy-benzyloxy)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride	398 (M^+; EI)
Example 91		Methyl (E)-4-[[3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenoxy]-methyl]benzoate dihydrochloride	426 (M^+; EI)
Example 92		(E)-2,3-Dihydro-1-methyl-5-[3-[(3,5-dimethyl-1-pyrazolyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride	387
Example 93		(E)-4'-[[3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzo-diazepin-5-yl)vinyl]phenoxy]-methyl]acetanilide hydrochloride	426

Example 94

(E)-5-[2-(4-Chlorophenoxy)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To a mixture of 56 mg (0.45 mmol) of 2-fluorobenzaldehyde and 64 mg (50 mmol) of 4-chlorophenol in 2.5 ml of dimethylformamide was added 75 mg (0.54

mmol) of sodium hydrogen carbonate. The mixture was heated at 95°C for 18 hours. To the mixture at ambient temperature was added 118 mg (0.36 mmol) of (8-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester followed by 25 mg (0.63 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred for 2 hours. The mixture was partitioned between 12 ml of water and 3 x 4 ml of dichloromethane. The combined organic portions were dried (magnesium sulphate), filtered and evaporated.The product was purified by column chromatography (20 g IST pre-packed column) eluting with ethyl acetate and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave a red gum which was recrystallised from acetone/ethyl acetate/diethyl ether to give 17 mg of (E)-5-[2-(4-chlorophenoxy)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as a red solid; MS: m/e 452 (M^+).

The starting material (8-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]-diazepin-5-ylidenemethyl)phosphonic acid diethyl ester was prepared in an analogous fashion to (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester, as described in Example 1 by replacing 2-fluorobenzoic acid with 2,4-difluorobenzoic acid.

Example 95

(E)-5-[3-Chloro-2-(3,4-dichlorobenzylthio)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To a mixture of 71 mg of 3-chloro-2-fluorobenzaldehyde (0.45 mmol) and 96 mg (0.45 mmol) of 3,4-dichlorobenzyl mercaptan in 3 ml of tetrahydrofuran was added 22 mg of sodium hydride (60% dispersion in mineral oil). After 3 hours 118 mg (0.36 mmol) of (8-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 94) was added followed by 25 mg (0.63 mmol) of sodium hydride (60% dispersion in mineral oil). The mixture was stirred for 1 hour. The product was purified by column chromatography (20 g IST pre-packed column) eluting with ethyl acetate and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave 113 mg of an orange gum which was recrystallised from methanol/acetone/petroleum ether (40-60°C) to give 44 mg of (E)-5-[3-chloro-2-

(3,4-dichlorobenzylthio)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: m/e 402 $(M)^+$.

Example 96

(E)-5-(2-Benzylthiostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

In a manner analogous to that described in Example 95, , by replacing 3,4-dichlorobenzyl mercaptan with benzyl mercaptan and 3-chloro-2-fluorobenzaldehyde with 2-fluorobenzaldehyde there was obtained (E)-5-(2-benzylthiostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride MS: m/e 504 (M^+).

Example 97

(E)-5-(2-Benzylthio-5-nitrostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

In an analogous fashion to Example 1 and by replacing (1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester with (8-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 94), and 3,4-difluorobenzaldehyde with 2-benzylthio-5-nitrobenzaldehyde there was obtained (E)-5-(2-benzylthio-5-nitrostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride; MS: m/e 448 (M^+H).

Example 98

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To 100 mg (0.24 mmol) of [8-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl]phosphonic acid diethyl ester in 2 ml of tetrahydrofuran was added 17 mg (0.42 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 44 mg (0.25 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 3 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/ethyl acetate and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave a red gum which was

recrystallized from ethyl acetate to give 25 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: m/e 436 (M^+).

The starting material was prepared as follows:

To 300 mg (0.77 mmol) of (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 41) in 1 ml of dioxane was added 123 mg (0.81 mmol) of 3-methoxyphenylboronic acid, 7.8 mg (0.028 mmol) of tricyclohexylphosphine, 10.5 mg 0.012 mmol)of tris-(dibenzylideneacetone)-palladium (0) and 141 mg of caesium fluoride. The mixture was heated at 80°C for 6 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was evaporated and the product was purified by column chromatography (20 g IST pre-packed column) eluting with acetone – petroleum ether (40 - 60°C) (1:2) to give 217 mg of [8-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl]phosphonic acid diethyl ester as a yellow gum; MS: m/e 417 (M^+).

Example 99

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-phenyl-1H-1,4-benzodiazepine dihydrochloride

To 105 mg (0.25 mmol) of (1-methyl-8-phenyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2 ml of tetrahydrofuran was added 18 mg (0.42 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 112 mg (0.64 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 18 hours. The product was purified by column chromatography (50 g IST pre-packed column) eluting with 2% methanol/dichloromethane and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallized from acetone/petroleum ether (40 -60°C) to give 40 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: m/e 406 (M^+).

The starting material was prepared as follows:

To 286 mg (0.83 mmol) of (8-chloro-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester

(prepared as described in Example 48)in 1 ml of dioxane was added 106 mg (0.87 mmol) of phenylboronic acid, 8.4 mg (0.03 mmol) of tricyclohexylphosphine, 11.5 mg 0.013 mmol)of tris-(dibenzylideneacetone)-palladium (0) and 152 mg of caesium fluoride. The mixture was heated at 80°C for 14 hours. The mixture was purified by column chromatography (20 g IST pre-packed column) eluting with acetone – petroleum ether (40 - 60°C) (1:2) to give 227 mg of (1-methyl-8-phenyl-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester as a yellow oil; MS: m/e 387 $[M+H]^+$.

Example 100

(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To 112 mg (0.27 mmol) of [8-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-ylidenemethyl]phosphonic acid diethyl ester (prepared as described in Example 98) in 2 ml of tetrahydrofuran was added 19 mg (0.47 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 70 mg (0.28 mmol) of 2-(4-chlorophenylthio)benzaldehyde was added and the mixture was stirred for 3 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/ethyl acetate and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated to leave an orange gum which was recrystallized from ethyl acetate to give 10 mg of (E)-5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride as a red solid; MS: m/e 510 (M^+).

Example 101

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride

To 105 mg (0.27 mmol) of (1-methyl-8-thiophen-3-yl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester in 2 ml of tetrahydrofuran was added 19 mg (0.47 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 49 mg (0.28 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 3 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/dichloromethane and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallized from acetone to give 75 mg of (E)-5-(3,4-dichlorostyryl)-2,3-

dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: 412 (M^+).

The starting material was prepared as follows:

To 300 mg (0.77 mmol) of (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 41) in 2 ml of dioxane was added 116 mg (0.81 mmol) of thiophene-3-boronic acid, 8 mg (0.028 mmol) of tricyclohexylphosphine, 10.8 mg 0.012 mmol)of tris-(dibenzylideneacetone)-palladium (0) and 140 mg of caesium fluoride. The mixture was heated at 80°C for 6 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was evaporated and the product was purified by column chromatography (20 g IST pre-packed column) eluting with acetone – petroleum ether (40 - 60°C) (1:3) to give 185 mg of (1-methyl-8-thiophen-3-yl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester as a yellow gum; MS: m/e 393 $[M+H]^+$.

Example 102

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-phenyl-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 101, by replacing (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester with (9-chloro-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 45) and thiophene-3-boronic acid with phenylboronic acid, there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-9-phenyl-1H-1,4-benzodiazepine hydrochloride as a red foam MS: m/e 393.2 $[M+H]^+$.

Example 103

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-(4-methoxyphenyl)-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 101, by replacing (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester by (9-chloro-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 45)

and thiophene-3-boronic acid by 4-methoxyphenylboronic acid, there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-9-(4-methoxyphenyl)-1H-1,4-benzodiazepine hydrochloride as a red foam MS: m/e 423.2 $[M+H]^+$.

Example 104

(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride

To 105 mg (0.27 mmol) of (1-methyl-8-thiophen-3-yl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 101) in 2 ml of tetrahydrofuran was added 19 mg (0.47 mmol) of sodium hydride (60% dispersion in mineral oil). After 10 minutes 70 mg (0.28 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 3 hours. The product was purified by column chromatography (20 g IST pre-packed column) eluting with 1% methanol/dichloromethane and treated with 0.15 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was recrystallized from ethyl acetate to give 32 mg of (E)-5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride as an orange solid; MS: m/e 486 (M^+).

Example 105

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-vinyl-1H-1,4-benzodiazepine dihydrochloride

To 123 mg (0.32 mmol) of (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 41) in 2 ml of dioxane was added 120 mg (0.38 mmol) of vinyl tributylstannane, followed by 11.1 mg (0.016 mmol)of palladium (II) bis-triphenylphosphine-dichloride. The mixture was heated at 80°C for 18 hours. To the mixture at ambient temperature was added 22 mg (0.55 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 57 mg (0.33 mmol) of 3,4-dichlorobenzaldehyde was added and the mixture was stirred for 18 hours. The sovent was removed and the product was purified by column chromatography eluting with 1 - 4% methanol/dichloromethane and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the

residue was dissolved from acetone/petroleum ether (40 60°C). The solvent was removed to give 25 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-8-vinyl-1H-1,4-benzodiazepine dihydrochloride as a red solid; MS: 357 (M^+).

Example 106

(E)-5-[2-(4-Chlorophenylthio)styryl]-8-(2-furyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

To 123 mg (0.32 mmol) of (8-bromo-1-methyl-1,2,3,4-tetrahydrobenzo[e][1,4]diazepin-5-ylidenemethyl)phosphonic acid diethyl ester (prepared as described in Example 41) in 2 ml of dioxane was added 135 mg (0.38 mmol) of 2-(tributylstannyl)furan, followed by 11.1 mg (0.016 mmol)of palladium (II) bis-triphenylphosphine-dichloride. The mixture was heated at 80°C for 18 hours. To the mixture at ambient temperature was added 55 mg (1.37 mmol) of sodium hydride (60% dispersion in mineral oil). After 5 minutes 82 mg (0.33 mmol) of 2-(4-chlorophenylthio)benzaldehyde was added and the mixture was stirred for 18 hours. The sovent was removed and the product was purified by column chromatography eluting with 24 - 40% acetone/petroleum ether (40 - 60°C) and treated with 0.10 ml of 4M hydrogen chloride in dioxan. The solvent was evaporated and the residue was dissolved from acetone/petroleum ether (40 60°C). The solvent was removed and the residue was recrystallised from acetone/petroleum ether (40 60°C) to give 63 mg of (E)-5-[2-(4-chlorophenylthio)styryl]-8-(2-furyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as dark red crystals; MS: m/e 471 (M^+).

Example 107

(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-1-methyl-2H-benzo-1,4-diazepin-2-one

65 mg (0.14 mmol) of (E)-N-[[N-[2-[3-(3,4-dichlorophenyl)acryloyl]phenyl]-N-methylcarbamoyl]methyl]pivalamide were dissolved in 5 ml of ethyl acetate saturated with hydrogen chloride and were stirred at room temperature for 30 minutes. The solvent was removed by evaporation and the residue dissolved in 5 ml of methanol and 40 mg (0.04 mmol) of triethylamine added. After 2 hours at room temperature the solvent was removed by evaporation and the residue chromatographed on silica gel using ethyl acetate/petrol 2:1 for the elution. There was obtained 33 mg of (E)-5-(3,4-dichlorostyryl)-1,3-dihydro-1-

methyl-2H-benzo-1,4-diazepin-2-one as a pale yellow foam. MS: m/e 344.9 $[M+H]^+$.

The starting material was prepared as follows:

i) 404 mg (2 mmol) of bromoacetyl bromide were added to a stirred, ice-cooled solution of 298 mg (2 mmol) of 2'-(methylamino)acetophenone in 5 ml of dichloromethane. The mixture was stirred for 20 minutes then 2 ml of 1M sodium hydroxide solution were added and stirring was continued for a further 15 minutes. The resulting solution was washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to dryness to give 2.1 g of 2'-acetyl-2-bromo-N-methylacetanilide as a viscous gum. ^{1}H NMR (400 MHz $CDCl_3$) δ: 2.54 (3H,s), 3.16 (3H,s), 3.45-3.52 (2H,q), 7.34 (1H,dd), 7.48 (1H,dt), 7.56 (1H,dt), 7.77 (1H,dd).

ii) 2.05 g (7.59 mmol) of 2'-acetyl-2-bromo-N-methylacetanilide and 2 g (30.77 mmol) of sodium azide were stirred in 20 ml of dimethylformamide at room temperature for 4 hours. The resulting mixture was diluted with water and extracted with diethyl ether. The organic phase was washed twice with water, dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol 5:3 for the elution. There was obtained 910 mg of 2'-acetyl-2-azido-N-methylacetanilide as a colourless gum. MS: m/e 233 $[M+H]^+$.

iii) 1.8 g (7.76 mmol) of 2'-acetyl-2-azido-N-methylacetanilide and 2 g (9.17 mmol) of di-tert-butyl dicarbonate were hydrogenated with 250 mg of 10% palladium on carbon in 50 ml of ethyl acetate for 45 minutes. The mixture was filtered, evaporated to dryness, dissolved in 5 ml of dichloromethane and left at room temperature for 24 hours. The solvent was removed by evaporation and the residue triturated with diethyl ether/petrol (1:1) and filtered. The filtrate was evaporated to dryness and chromatographed on silica gel using ethyl acetate/petrol (55:45) to give 171 mg of N-[[N-(2-acetylphenyl)-N-methylcarbamoyl]methyl]pivalamide as a gum. MS: m/e 307 $[M+H]^+$.

iv) 5 drops of 3M sodium hydroxide solution were added to a mixture of 160 mg (0.52 mmol) of N-[[N-(2-acetylphenyl)-N-methylcarbamoyl]methyl]pivalamide and 100 mg (0.57 mmol) of 3,4-dichlorobenzaldehyde in 3 ml of methanol. After

1 hr at room temperature the solvent was removed by evaporation and the residue chromatographed on silica gel using ethyl acetate/petrol (55:45) for the elution. There was obtained 65 mg of (E)-N-[[N-[2-[3-(3,4-dichlorophenyl)acryloyl]phenyl]-N-methylcarbamoyl]methyl]pivalamide as a yellow gum. MS: m/e 463 $[M+H]^+$.

Example 108

(E)-1,3-Dihydro-5-styryl-2H-benzo-1,4-diazepin-2-one

In an analogous manner to Example 107 but replacing 2'-(methylamino)acetophenone with 2'-aminoacetophenone and 3,4-dichlorobenzaldehyde with benzaldehyde there was obtained (E)-1,3-dihydro-5-styryl-2H-benzo-1,4-diazepin-2-one as an off-white solid MS: m/e 263.4 $[M+H]^+$.

Example 109

(E)-5-(2,3-Dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

In an analogous manner to Example 107 but replacing 2'-(methylamino)acetophenone with 2'-aminoacetophenone and 3,4-dichlorobenzaldehyde with 2,3-dichlorobenzaldehyde there was obtained (E)-5-(2,3-dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one as a light yellow solid MS: m/e 331.1 $[M+H]^+$.

Example 110

(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

In an analogous manner to Example 107 but replacing 2'-(methylamino)acetophenone with 2'-aminoacetophenone there was obtained (E)-5-(3,4-dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one as an off white solid, MS: m/e 331.1 $[M+H]^+$.

Example 111

(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride

In an analogous manner to Example 107 but replacing 3,4-dichlorobenzaldehyde with 2-(4-chlorophenylthio)benzaldehyde there was

obtained (E)-5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride as a red solid MS: m/e 391.2 $[M+H]^+$.

Example 112

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine dihydrochloride

1.3 g (4.41 mmol) of (E)-3-(3,4-dichlorophenyl)-1-(2-fluorophenyl)propenone were refluxed in a mixture of 5 ml of ethylenediamine and 10 ml of pyridine for 17 hours. The solvent was removed by evaporation and the residue chromatographed on silica gel using dichloromethane/methanol (92:8) for the elution. The product was added to a mixture of ethyl acetate and 2M hydrochloric acid and the solid filtered off and recrystallized from ethanol/acetone to give 35 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine dihydrochloride as a red solid. MS: m/e 316.9 $[M+H]^+$.

The starting material was prepared as follows:

0.2 ml of 3M sodium hydroxide solution were added to a solution of 1.38 g (10 mmol) of 2-fluoroacetophenone and 1.75 g (10 mmol) of 3,4-dichlorobenzaldehyde in 20 ml of ethanol. After 30 minutes the solid was filtered off and washed with ethanol and petrol to give 1.49 g of (E)-3-(3,4-dichlorophenyl)-1-(2-fluorophenyl)propenone as a white solid. ^1H NMR (400 MHz $CDCl_3$) 7.08-7.58 (8H,m), 7.75-7.85 (1H,dt).

Example 113

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-benzo-1,4-diazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-methylethylenediamine there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-benzo-1,4-diazepine dihydrochloride as a red solid MS: m/e 331 $[M+H]^+$.

Example 114

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine

In an analogous manner to Example 112 but replacing 2-fluoroacetophenone with 2-fluoro-4-(RS)-pyranyloxyacetophenone and ethylenediamine with N-methylethylenediamine there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine as a dark red solid MS: m/e 431.2 $[M+H]^+$.

Example 115

(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine

In an analogous manner to Example 112 but replacing 2-fluoroacetophenone with 2-fluoro-4-(RS)-pyranyloxyacetophenone and ethylenediamine with N-methylethylenediamine and 3,4-dichlorobenzaldehyde with 2-(4-chlorophenylthio)benzaldehyde there was obtained (E)-5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine as a yellow foam MS: m/e 505.2 $[M+H]^+$.

Example 116

tert-Butyl (E)-[5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]carbamate

In an analogous manner to Example 112 but replacing 2-fluoroacetophenone with (3-Acetyl-4-fluorophenyl)carbamic acid tert-butyl ester and ethylenediamine with N-methylethylenediamine there was obtained tert-butyl (E)-[5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]carbamate as a light brown solid MS: m/e 446.2 $[M+H]^+$.

The (3-acetyl-4-fluorophenyl)carbamic acid tert-butyl ester starting material was prepared as follows.

To a solution of 1.19g (7.77 mmol) of 1-(5-amino-2-fluorophenyl)ethanone in 18 ml of dry tetrahydrofuran at room temperature under an atmosphere of nitrogen was added 1.86 g (8.54 mol) of tert-butyl dicarbonate. The solution was stirred for

28 hours at room temperature followed by 17 hours at 45°C, cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with sodium bicarbonate solution, dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol 4:1 for the elution. There was obtained 1.45 g of (3-acetyl-4-fluorophenyl)carbamic acid tert-butyl ester MS: m/e 271 $[M+CH_3CN]^+$.

Example 117

(E)-5-(3,4-Dichlorostyryl)-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-ethylethylenediamine there was obtained (E)-5-(3,4-dichlorostyryl)-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride as a dark red solid. MS: m/e 344.9 $[M+H]^+$.

Example 118

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-propyl-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-propylethylenediamine there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-propyl-1H-1,4-benzodiazepine dihydrochloride as a dark red solid MS: m/e 359 $[M+H]^+$.

Example 119

(E)-1-Benzyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-benzylethylenediamine there was obtained (E)-1-benzyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride as a red solid. MS: m/e 406.9 $[M+H]^+$.

Example 120

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-ethanol dihydrochloride

In analogous manner to Example 112 but replacing ethylenediamine with 2-(2-aminoethylamino)ethanol there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-ethanol dihydrochloride as a red solid MS: m/e 360.9 $[M+H]^+$.

Example 121

(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-methylethylenediamine and 3,4-dichlorobenzaldehyde with 2-(4-chlorophenylthio)benzaldehyde there was obtained (E)-5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as a red solid. MS: m/e 405 $[M+H]^+$.

Example 122

(E)-5-(3,4-Dichlorostyryl)-6-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 112 but replacing ethylenediamine with N-methylethylenediamine and 2-fluoroacetophenone with 2-fluoro-6-trifluoromethylacetophenone there was obtained (E)-5-(3,4-dichlorostyryl)-6-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride as a light orange solid. MS: m/e 398.9 $[M+H]^+$.

Example 123

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-isopropyl-1H-1,4-benzodiazepine dihydrochloride

A mixture of 1.475 g (5 mmol) of (E)-3-(3,4-dichlorophenyl)-1-(2-fluorophenyl)propenone and 1.1 g (5.45 mmol) of N-[2-(isopropylamino)ethyl]pivalamide was refluxed in 10 ml of pyridine for 6 hours.

The solvent was removed by evaporation and the residue dissolved in water and ethyl acetate. The organic phase was dried over magnesium sulphate, evaporated to dryness, triturated with ethanol and filtered. After evaporation the filtrate was chromatographed on silica gel using ethyl acetate/petrol (1:4) for the elution then chromatographed again using dichloromethane/methanol (49:1) to give 26 mg of a yellow gum which was added to a solution of 50 mg (0.26 mmol) of 4-toluenesulphonic acid in 5 ml of acetonitrile and refluxed for 30 seconds. The solvent was removed by evaporation and the residue dissolved in 5 ml of methanol and 50 mg (0.5 mmol) of triethylamine added. After refluxing for 1 minute the solvent was removed and the residue dissolved in saturated sodium bicarbonate solution and ethyl acetate. The organic phase was dried over magnesium sulphate, filtered, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate for the elution. The product was dissolved in a solution of hydrogen chloride in ethyl acetate, evaporated to dryness, redissolved in a small volume of ethyl acetate and allowed to crystallize. There was obtained 7 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-isopropyl-1H-1,4-benzodiazepine dihydrochloride as an orange solid. MS: m/e 359 $[M+H]^+$.

The starting material was prepared as follows:

6.54 g (30 mmol) of di-tert-butyl dicarbonate in 30 ml of tetrahydrofuran were added dropwise over 30 minutes to an ice-cooled, stirred solution of 5.1 g (50 mmol) of N-isopropylethylenediamine in 100 ml of tetrahydrofuran. The mixture was stirred at room temperature for 3 hours then evaporated to dryness. The residue was dissolved in diethyl ether and water and the organic phase dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using dichloromethane/methanol/ acetic acid/water (120:15:3:2) for the elution. There was obtained 3.6 g of N-[2-(isopropylamino)ethyl]pivalamide as a colourless oil. ^{1}H NMR (400 MHz, CDCl3) δ: 1.01 (6H,d), 1.41 (9H,s), 2.69 (2H,t), 2.75 (1H,m), 3.18 (2H,q), 4.92 (1H,br.s)

Example 124

(E)-1-Acetyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride

50 mg (0.158 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine were dissolved in a mixture of 0.1 ml of acetic anhydride and 1 ml of pyridine by heating to 80°C. The mixture was left to cool for 30 minutes then evaporated to dryness and the residue dissolved in water and ethyl acetate. The organic phase was dried over magnesium sulphate, filtered, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate for the elution. The product was dissolved in a solution of hydrogen chloride in ethyl acetate, evaporated to dryness and the residue dissolved in a small volume of acetone and left to crystallize. There was obtained 12 mg of (E)-1-acetyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride as an off-white solid. MS: m/e 358.9 $[M+H]^+$.

Example 125

(E)-1-Benzoyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride

In an analogous manner to Example 124 but replacing acetic anhydride with benzoic anhydride there was obtained (E)-1-benzoyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride as an off-white solid. MS: m/e 420.9 $[M+H]^+$.

Example 126

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-(4-nitrobenzyl)-1H-1,4-benzodiazepine dihydrochloride

A mixture of 117 mg (0.3 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine dihydrochloride, 70 mg (0.32 mmol) of 4-nitrobenzyl bromide and 127 mg (1.2 mmol) of sodium carbonate were heated at 70°C in 3 ml of ethanol for 18 hours. The mixture was diluted with ethyl acetate and water and the organic phase dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed three times on silica gel using ethyl acetate/petrol (3:1), dichloromethane/methanol (97:3) and ethyl acetate/petrol

(9:1) for the elutions. The product was dissolved in a solution of hydrogen chloride in methanol, evaporated to dryness and the residue triturated with diethyl ether to give 12 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-(4-nitrobenzyl)-1H-1,4-benzodiazepine dihydrochloride. MS: m/e 451.9 $[M+H]^+$.

Example 127

Methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate dihydrochloride

In an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with methyl 4-(bromomethyl)benzoate there was obtained methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate dihydrochloride as a red solid. MS: m/e 465 $[M+H]^+$.

Example 128

Methyl (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride

In an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with methyl 3-(bromomethyl)benzoate there was obtained methyl (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride as a dark orange solid MS: m/e 465.2 $[M+H]^+$.

Example 129

Methyl (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride

In an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with methyl 2-(bromomethyl)benzoate there was obtained methyl (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride as a dark orange solid MS: m/e 465.2 $[M+H]^+$.

Example 130

Methyl (E)-4-[[5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride

In an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with methyl 4-(bromomethyl)benzoate and replacing 3,4-dichlorobenzaldehyde with 2-(4-chlorophenylthio)benzaldehyde there was obtained methyl (E)-4-[[5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride as a dark orange solid MS: m/e 539.2 $[M+H]^+$.

Example 131

(E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-[(2-naphthyl)methyl]-1H-1,4-benzodiazepine dihydrochloride

In an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with 2-(bromomethyl)naphthalene there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-[(2-naphthyl)methyl]-1H-1,4-benzodiazepine dihydrochloride as a red solid. MS: m/e 457 $[M+H]^+$.

Example 132

(E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid dihydrochloride

0.4 ml of 1M potassium hydroxide solution were added to a solution of 80 mg (0.17 mmol) of methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate in 8 ml of methanol. The mixture was heated at 60°C for 4 hours then left at room temperature for 3 days. A further 0.2 ml of 1M potassium hydroxide solution were added followed by heating at 60°C for 4 hours. The solvent was removed by evaporation and the residue dissolved in diethyl ether and water. The aqueous phase was separated, acidified with acetic acid and extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (120:15:3:2) for the elution. The product was dissolved in a mixture of 10 ml of acetone and 0.2 ml of concentrated hydrochloric acid, evaporated to

dryness and the residue triturated with diethyl ether. There was obtained 55 mg of (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid dihydrochloride MS: m/e 451 $[M+H]^+$.

Example 133

(E)-3-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride

In an analogous manner to Example 132 but replacing methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate with methyl (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate there was obtained (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride as a dark red solid MS: m/e 451 $[M+H]^+$.

Example 134

(E)-2-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride

In an analogous manner to Example 132 but replacing methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate with methyl (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate there was obtained (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride as a red solid. MS: m/e 451.2 $[M+H]^+$.

Example 135

(E)-4-[[5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride

In an analogous manner to Example 132 but replacing methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate with methyl (E)-4-[[5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride there was obtained (E)-4-[[5-[2-(4-chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloridehydrochloride as a dark orange solid. MS: m/e 525.2 $[M+H]^+$.

Example 136

(E)-5-(3,4-Dichlorostyryl)-N-ethyl-2,3-dihydro-1H-1,4-benzodiazepine-1-carboxamide

A solution of 32 mg (0.1 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine and 10 mg (0.14 mmol) of ethyl isocyanate was heated at 85°C for 48 hours, a further 10 mg of ethyl isocyanate being added after 6 hours and again after 30 hours. The solvent was removed by evaporation and the residue chromatographed on silica gel using dichloromethane/methanol (19:1) for the elution. The product was recrystallized from diethyl ether. There was obtained 16 mg of (E)-5-(3,4-dichlorostyryl)-N-ethyl-2,3-dihydro-1H-1,4-benzodiazepine-1-carboxamide as an off-white solid. MS: m/e 387.9 $[M+H]^+$.

Example 137

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid

0.5 ml of 1M sodium hydroxide solution were added to a solution of 113 mg (0.28 mmol) of ethyl (E)-2-[5-(3,4-dichlorostyryl)-2,3-dihydro-1,4-benzodiazepin-1-yl]acetate in 3 ml of ethanol and the mixture left at room temperature for 1.5 hours. The solvent was removed by evaporation and the residue dissolved in water and washed with diethyl ether. The aqueous layer was acidified with acetic acid and a red gum separated out. The gum was dissolved in a small amount of ethanol and diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulphate, filtered and evaporated to dryness to give 88 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid as a red solid. MS: m/e 374.9 $[M+H]^+$.

The starting material was prepared in an analogous manner to Example 126 but replacing 4-nitrobenzyl bromide with ethyl bromoacetate there was obtained ethyl (E)-2-[5-(3,4-dichlorostyryl)-2,3-dihydro-1,4-benzodiazepin-1-yl]acetate as an orange gum. MS: m/e 402.9 $[M+H]^+$.

Example 138

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-N-(2-methoxyethyl)-1H-1,4-benzodiazepine-1-acetamide dihydrochloride

A mixture of 33 mg (0.088 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid, 30 mg (0.157 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 16 mg (0.105 mmol) of 1-hydroxybenzotriazole hydrate and 14 mg (0.187 mmol) of 2-methoxyethylamine was stirred in 3 ml of dichloromethane for 3 hours. The solution was washed with saturated sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed three times on silica gel using dichloromethane/methanol (94:6), dichloromethane/methanol 92:8) and ethyl acetate/methanol (9:1) for the elutions. The product was dissolved in a solution of hydrogen chloride in ethyl acetate, evaporated to dryness and the residue triturated with diethyl ether. There was obtained 5 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-N-(2-methoxyethyl)-1H-1,4-benzodiazepin-1-acetamide dihydrochloride as a red solid. MS: m/e 431.9 $[M+H]^+$.

Example 139

Ethyl (E)-6-(3,4-dichlorostyryl)-4H-imidazo[1,5-a]benzodiazepine-3-carboxylate

100 mg (2.5 mmol) of 60% sodium hydride disperion in mineral oil were added to a solution of 728 mg (2.2 mmol) of (E)-5-(3,4-dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 5 ml of anhydrous dimethylformamide at room temperature under a nitrogen atmosphere and stirred for 30 minutes. The mixture was cooled to -20°C, 431 mg (2.5 mmol) of diethyl chlorophosphate were added and stirring was continued for a further 30 minutes at -10°C before being added to a solution prepared by addition of 1.65 ml (3.3 mmol) of 2M lithium diisopropylamide to a solution of 375 mg(3.32 mmol) of ethyl isocyanoacetate in 5 ml of anhydrous tetrahydrofuran at -78°C under a nitrogen atmosphere. The resulting mixture was stirred at -78°C for 2 hours then warmed to -30°C and 180 mg (3 mmol) of acetic acid were added followed by water and ethyl acetate. The organic phase was washed twice with water, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel using ethyl acetate/methanol (49:1) for the elution. The product was dissolved in

1 ml of ethyl acetate and 10 ml of diethyl ether and left to crystallize. There was obtained 116 mg of ethyl (E)-6-(3,4-dichlorostyryl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate as a light-brown solid. MS: m/e 425.9 $[M+H]^+$.

Example 140

(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoic acid acetate

2.2 ml of 2M potassium hydroxide solution were added to a solution of 770 mg (2.41 mmol) of methyl (E)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoate in 22ml of methanol. The temperature was raised to 60°C and the solution was stirred for 3 hours. A further 2ml of 2M potassium hydroxide solution was added and the solution was stirred for a further 16 hours. The solvent was removed by evaporation and the residue dissolved in water and washed with diethyl ether. The aqueous layer was acidified with acetic acid and extracted three times with ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered and evaporated to dryness. There was obtained (E)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoic acid acetate as a red oil, MS: m/e 307.2 $[M+H]^+$.

The starting material was prepared by analogy to Example 1 replacing 3,4-difluorobenzaldehyde with methyl-4-formyl benzoate

Example 141

(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(4-methoxybenzyl)benzamide hydrochloride

A mixture of 50 mg (0.164 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid, 38 mg (0.199 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 27 mg (0.199 mmol) of 1-hydroxybenzotriazole hydrate and 0.021 ml (0.145 mmol) of 4-methoxybenzylamine was stirred in 5 ml of dichloromethane for 3 hours at room temperature and then left to stand at 4°C for 54 hours. The solution was diluted with dichloromethane and then sequentially washed with citric acid, saturated sodium bicarbonate solutionand brine, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed twice on silica gel

using sequentially dichloromethane/methanol (98:2), dichloromethane/methanol (97:3) and dichloromethane/methanol (95:5) for the elutions. The product was dissolved in a solution of hydrogen chloride in ether and evaporated to dryness. There was obtained 9 mg of (E)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(4-methoxybenzyl)benzamide hydrochloride as a red oil MS: m/e 426.3 $[M+H]^+$.

Example 142

(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxybenzyl)benzamide hydrochloride

In an analogous manner to Example 141 but replacing 4-methoxybenzylamine with 3-methoxybenzylamine there was obtained (E)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxybenzyl)-benzamide hydrochloride as a red oil MS: m/e 426.1 $[M+H]^+$.

Example 143

(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxybenzyl)benzamide hydrochloride

In an analogous manner to Example 141 but replacing 4-methoxybenzylamine with 2-methoxybenzylamine there was obtained (E)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxybenzyl)-benzamide hydrochloride as a red oil MS: m/e 426.0 $[M+H]^+$.

Example 144

tert-Butyl (E)-[2-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)-vinyl]-benzamido]ethyl)]carbamate

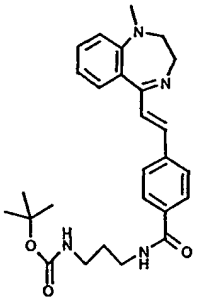
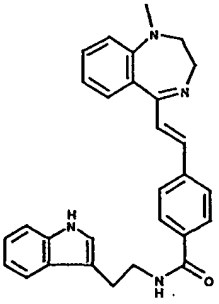
In an analogous manner to Example 1 but replacing 3,4-difluorobenzaldehyde with [2-(4-formyl-benzoylamino)-ethyl]carbamic acid tert-butyl ester there was obtained tert-butyl (E)-[2-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)-vinyl]-benzamido]ethyl)]carbamate as a light yellow glass MS: m/e 449.1 $[M+H]^+$.

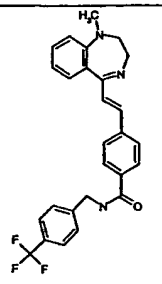
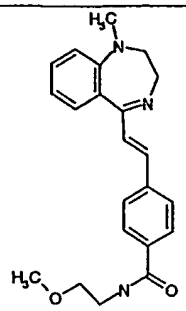
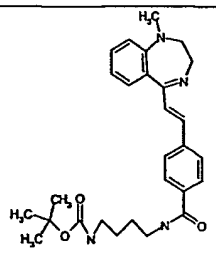
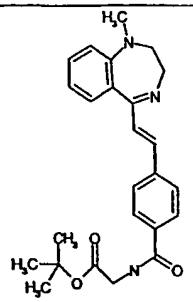
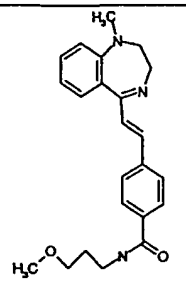
The starting material was prepared as follows

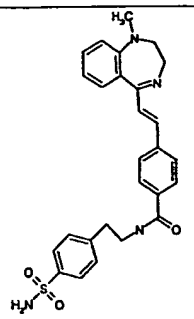
A mixture of 100 mg (0.67 mmol) of 4-carboxybenzaldehyde, 153 mg (0.798 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 106 mg (0.67 mmol) of N-(2-aminoethyl)carbamic acid tert-butyl ester was stirred in 5 ml of dichloromethane for 16 hours at room temperature. The solution was diluted with dichloromethane and then sequentially washed with citric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulphate, filtered and evaporated to dryness. There was obtained 184 mg of[2-(4-formylbenzoylamino)ethyl]carbamic acid tert-butyl ester as a colourless oil MS: m/e 316 $[M+Na]^+$.

In a manner analogous to that described in Example 144, starting with 4-carboxybenzaldehyde, and the appropriate amine, the compounds shown in Table 12 were also prepared:

Table 12

Compound	Structure	Name	MS (ES) (M+H)+
Example 145		tert-Butyl (E)-[3-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido] propyl]carbamate	463.4
Example 146		(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(1H-indol-3-yl)ethyl]benzamide	449.1

Example 147		(E)-N-[4-(Trifluoromethyl)benzyl]-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide	464.3
Example 148		(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxyethyl)benzamide	364.0
Example 149		tert-Butyl (E)-(4-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]butyl)carbamate	477.1
Example 150		tert-Butyl (E)-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]acetate	306.1 (M+H-Boc)
Example 151		(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxypropyl)benzamide	378.3

Example 152		(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(4-sulfamoylphenyl)ethyl]benzamide	489.1

Example 153

N-(2-Aminoethyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride

A few drops of a saturated solution of hydrogen chloride in diethyl ether were added to a solution of 15 mg (0.033 mmol) (tert-butyl (E)-[2-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)-vinyl]-benzamido]ethyl)]carbamate. The mixture was stirred at room temperature for 16 hours and the resultant solid filtered off, dissolved in methanol and evaporated.. There was obtained 8mg of N-(2-aminoethyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride as a dark red gum MS: m/e 349.0 $[M+H]^+$.

Example 154

(E)-N-(3-Aminopropyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride

In an analogous manner to Example 153, starting with tert-butyl (E)-[3-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]propyl]carbamate, there was obtained (E)-N-(3-aminopropyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride as a dark red glass MS: m/e 363.3 $[M+H]^+$.

Example 155

(E)-N-(4-Aminobutyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride

In an analogous manner to Example 153, starting with tert-butyl (E)-(4-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]butyl)carbamate, there was obtained (E)-N-(4-Aaminobutyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride as a red glass MS: m/e 377.3 $[M+H]^+$.

Example 156

4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride

In an analogous manner to Example 153, starting with tert-butyl (E)-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]acetate, there was obtained 4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride as a dark red glass MS: m/e 306.2 $[M+H]^+$.

Example 157

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-ol hydrochloride

To a solution of 74 mg (0.17 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine (prepared in Example 114) in methanol (5 ml) was added 33 mg (0.17mmol) p-toluenesulphonic acid and the solution stirred at room temperature for 1 hour. A further 33 mg (0.17 mmol) of p-toluenesulphonic acid was added and the solution stirred for a further 2 hours. The solvent was removed by evaporation and the residue partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel using first dichloromethane/methanol (95:5), and then dichloromethane/methanol (9:1) for the elution. The product was dissolved in a solution of hydrogen chloride in ether and evaporated to dryness. After trituration there was obtained 8 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-

methyl-1H-1,4-benzodiazepin-8-ol hydrochloride as a dark orange solid MS: m/e 347.2 $[M+H]^+$.

Example 158

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thenyloxy)-1H-1,4-benzodiazepine

To a stirred solution of 50 mg (0.14mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-ol (prepared as described in Example 157) in 5 ml of dry tetrahydrofuran was added 0.014ml (0.14 mmol) of thiophene-2-methanol and 0.053 ml (0.21 mmol) of tributylphosphine. The solution was cooled, under an atmosphere of nitrogen, to 0°C and 37 mg (0.21 mmol) of 1,1'-azobis(N,N-dimethylformamide) was added. The mixture was allowed to warm up to room temperature and then stirred for 16 hours. A further 0.053 ml (0.21 mmol) of tributylphosphine and 37 mg (0.21 mmol) of 1,1'-azobis(N,N-dimethylformamide) were added and the mixture stirred for a further 4 hours. The mixture was filtered and the filtrate evaporated and then chromatographed on silica gel using dichloromethane/methanol (98:2) for the elution. There was obtained 4.2 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thenyloxy)-1H-1,4-benzodiazepine as an orange gum MS: m/e 442.8 $[M+H]^+$.

Example 159

Methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-yloxy]methyl]benzoate diacetate

In an analogous fashion to Example 158, replacing thiophene-2-methanol by 4-hydroxymethylbenzoic acid, there was obtained 30mg of methyl (E)-4-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-yloxy]methyl]benzoate diacetate as a dark red gum MS: m/e 495.2 $[M+H]^+$.

Example 160

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride

To a solution of 11 mg (0.025 mmol) of tert-butyl (E)-[5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]carbamate in 0.5 ml of acetonitrile and 1 drop of anisole was added 1 drop of trifluoroacetic acid. The solution was stirred for 20 minutes, concentrated under reduced

pressure and the residue partitioned between brine and dichloromethane. The organic phase was dried over magnesium sulphate, filtered and evaporated, redissolved in a solution of hydrogen chloride in ethyl acetate and the solvent removed to afford 7.9 mg of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride as a red solid MS: m/e 346.2 $[M+H]^+$.

Example 161

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-acetamide hydrochloride

To a solution of 43 mg , 0.125 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride in 3 ml of dichloromethane was added 0.05 ml, 0.626 mmol) of pyridine, and 0.02 ml of acetic anhydride (0.15 mmol). The solution was stirred for 4 hours, concentrated under reduced pressure and the residue partitioned between brine and dichloromethane. The organic phase was dried over magnesium sulphate, filtered and evaporated, The residue was chromatographed on silica gel using first dichloromethane/methanol (98:2) and then dichloromethane/methanol (97:3) for the elution. The product was redissolved in a solution of hydrogen chloride in ethyl acetate and the solvent removed to afford (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-acetamide hydrochloride as a dark red solid MS: m/e 388.2 $[M+H]^+$.

Example 162

(E)-N-[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]methanesulfonamide

To a solution of 100 mg , 0.219 mmol) of (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride in 3 ml of dichloromethane was added 0.073 ml, 0.9 mmol) of pyridine, and 0.018 ml, (0.231 mmol) of methanesulphonyl chloride. The solution was stirred for 1 hour, concentrated under reduced pressure and the residue partitioned between brine and dichloromethane. The organic phase was dried over magnesium sulphate, filtered and evaporated, The residue was chromatographed on silica gel using first dichloromethane/methanol (98:2) and then dichloromethane/methanol (97:3) for the elution. There was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-acetamide hydrochloride as a brown solid MS: m/e 424.1 $[M+H]^+$.

Example 163

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(4-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine

In an analogous fashion to Example 101, by replacing thiophene-3-boronic acid by 4-methoxyphenylboronic acid, there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-8-(4-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine as a red solid MS: m/e 473.2 $[M+H]^+$.

Example 164

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thienyl)-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 101, by replacing thiophene-3-boronic acid with thiophene-2-boronic acid, there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thienyl)-1H-1,4-benzodiazepine hydrochloride as a red solid MS: m/e 413.1 $[M+H]^+$.

Example 165

(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-amine hydrochloride

In an analogous fashion to Example 83, from (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-8-nitro-1H-1,4-benzodiazepine hydrochloride, there was obtained (E)-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-amine hydrochloride as a red solid MS: m/e 346.2 $[M+H]^+$.

Example 166

Methyl (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate

In an analogous fashion to Example 126, using methyl 4-(bromomethyl)benzoate, and 4-(3-bromophenyl)-2-formyl-pyridine there was obtained methyl (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate as a light yellow solid, MS: m/e 588.1 $[M+H]^+$.

Example 167

Methyl (E)-4-[[5-(2-benzylthio-5-nitrostyryl)-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate

In an analogous fashion to Example 126, using methyl 4-(bromomethyl)benzoate, and 2-benzylthio-5-nitrobenzaldehyde there was obtained methyl (E)-4-[[5-(2-benzylthio-5-nitrostyryl)-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate as a light yellow solid, MS: m/e 598.2 $[M+H]^+$.

Example 168

(E)-4-[[5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride

In an analogous fashion to Example 132, from methyl (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate, there was obtained (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride as a red solid, MS: m/e 574.2 $[M+H]^+$.

Example 169

(E)-9-(3,4-Dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo[4,5-h][1,4]benzodiazepin-6-one

In an analogous fashion to Example 112, by replacing 2-fluoroacetophenone with 1-(6-fluoro-benzo[1,3]dioxol-5-yl)-ethanone there was obtained (E)-9-(3,4-dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo[4,5-h][1,4]benzodiazepin-6-one as a red solid, MS: m/e 374.9 $[M+H]^+$.

Example 170

(E)-9-(3,4-Dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo[4,5-h][1,4]benzodiazepin-6-one

In an analogous fashion to Example 112, by replacing 2-fluoroacetophenone with 1-(2-fluoro-4,5-dimethoxy-phenyl)ethanone there was obtained (E)-9-(3,4-dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo[4,5-h][1,4]benzodiazepin-6-one as a red solid, MS: m/e 390.9 $[M+H]^+$.

Example 171

(E)-2,3-Dihydro-5-(4-methoxystyryl)-1-methyl-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 1, replacing 3,4-difluorobenzaldehyde with 4-methoxybenzaldehyde, there was obtained (E)-2,3-dihydro-5-(4-methoxystyryl)-1-methyl-1H-1,4-benzodiazepine hydrochloride as a dark red solid, MS: m/e 293.2 $[M+H]^+$.

Example 172

(E)-2,3-Dihydro-1-methyl-5-(4-phenoxystyryl)-1H-1,4-benzodiazepine hydrochloride

In an analogous fashion to Example 1, replacing 3,4-difluorobenzaldehyde with 4-phenoxybenzaldehyde, there was obtained (E)-2,3-dihydro-5-(4-methoxystyryl)-1-methyl-1H-1,4-benzodiazepine hydrochloride as a red oil, MS: m/e 355.3 [M+H]+.

Example 173

(E)-2,3-Dihydro-1-methyl-5-styryl-1H-1,4-benzodiazepine dihydrochloride

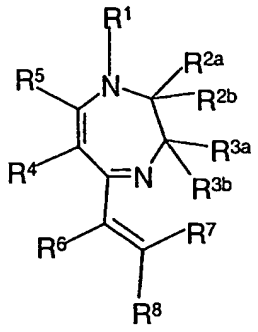
In an analogous manner to Example 107 but replacing 3,4-dichlorobenzaldehyde with benzaldehyde there was obtained (E)-2,3-dihydro-1-methyl-5-styryl-1H-1,4-benzodiazepine dihydrochloride as a red solid MS: m/e 263.0 $[M+H]^+$.

In the present specification "comprise" means "includes or consists of" and "comprising" means "including or consisting of".

The features disclosed in the foregoing description, or the following claims, or the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

Claims

1. Compounds of the general formula



I

wherein

R^1 is H, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl,

lower alkyl carbonyl, aryl carbonyl, lower alkyl amino carbonyl, aryl amino carbonyl,

lower alkoxy carbonyl,

aryloxy carbonyl,

R^{2a}, R^{2b} independently are H or lower alkyl or

R^{2a} and R^{2b} together are oxo,

R^1 and R^{2a} or R^{2b} together with the nitrogen and the carbon atom to which they are attached

form an optionally substituted heterocycle;

R^{3a}, R^{3b} independently are H or lower alkyl

R^4 and R^5 together with the two carbon atoms to which they are attached form an optionally

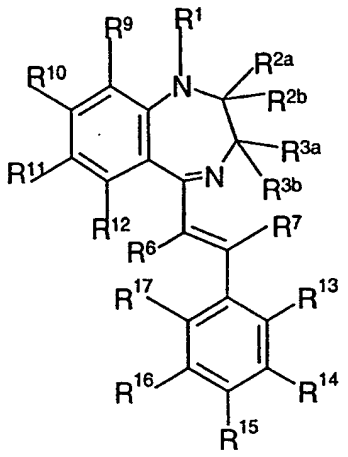
substituted aryl or an optionally substituted heterocycle,

R^6 and R^7 is H or lower alkyl and

R^8 is optionally substituted aryl or heterocyclyl

or pharmaceutically acceptable salts thereof.

2. Compounds of claim 1, as defined by the general formula



II

wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 are as above and

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are H, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl,

aryl, heterocyclyl,

carboxyl, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxyl,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino, alkyl carbonyl amino alkyl carbonyl amino, dialkyl amino carbonyl amino alkyl carbonyl amino, cycloalkyl carbonyl amino alkyl carbonyl amino, aryl carbonyl amino alkyl carbonyl amino and heterocyclyl carbonyl amino alkyl carbonyl amino, alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino,
nitro,

alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,

thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

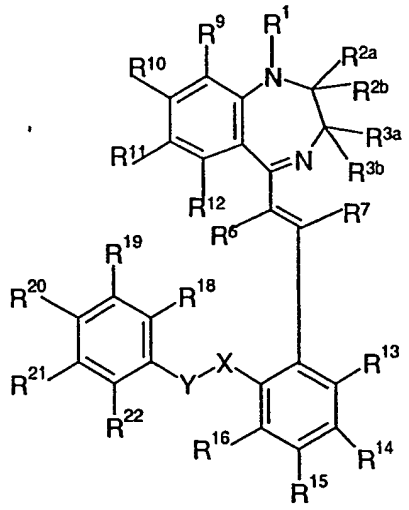
halogen

or

R^{10} and R^{11} together with the two carbon atoms to which they are attached form optionally

substituted aryl or an optionally substituted heterocycle or pharmaceutically acceptable salts thereof.

3. Compounds of claim 1 or 2 as defined by the general formula



III

wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are as above and wherein

X is $(CH_2\text{-})_n$ with n being an integer between 0 and 3, -S-, -O- or NR^{23}-, wherein R^{23} is H or lower alkyl,

Y is $-(CH_2\text{-})_n$ with n being an integer between 0 and 3, and when X is $(CH_2\text{-})_n$ with n being an integer between 0 and 3 then Y is S, O or $-NR^{23}$ wherein R^{23} is as above,

R^{18}, R^{19}, R^{20} and R^{22} independently are H, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl,

aryl, heterocyclyl,

carboxyl, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxyl,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino,
alkyl carbonyl amino alkyl carbonyl amino, dialkyl amino carbonyl amino alkyl carbonyl amino, cycloalkyl carbonyl amino alkyl carbonyl amino, aryl carbonyl amino alkyl carbonyl amino and heterocyclyl carbonyl amino alkyl carbonyl amino,
alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino,
nitro,

alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,

thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

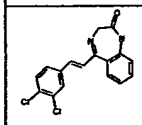
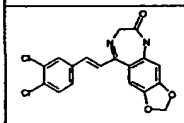
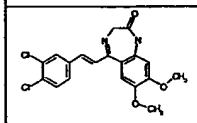
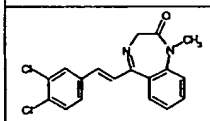
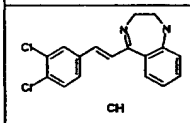
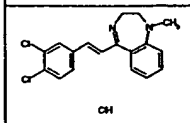
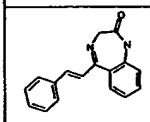
halogen

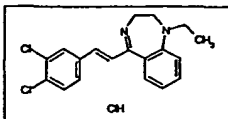
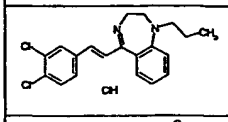
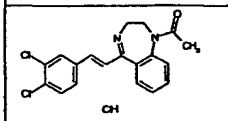
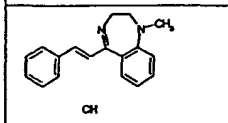
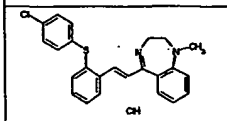
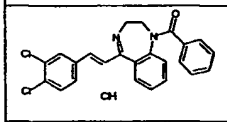
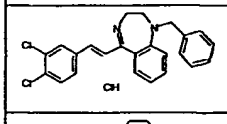
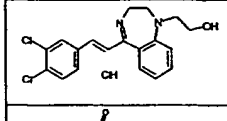
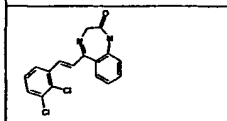
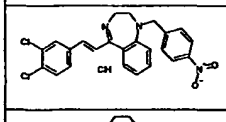
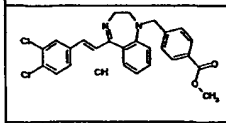
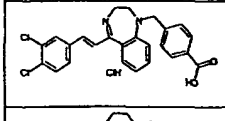
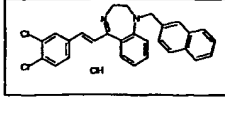
or pharmaceutically acceptable salts thereof.

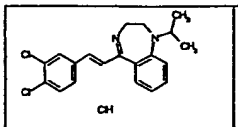
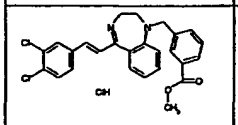
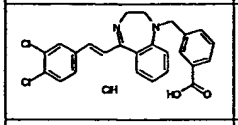
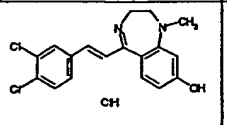
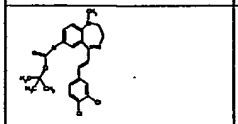
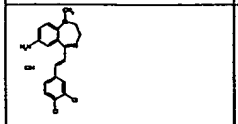
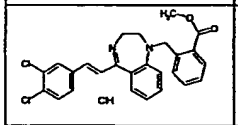
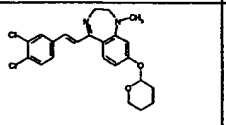
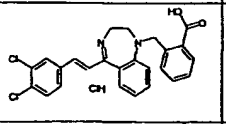
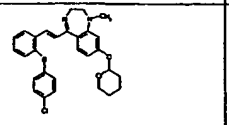
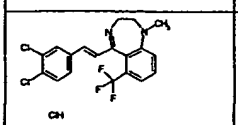
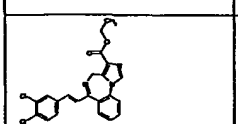
4. A compound of any one of claims 1 to 3, wherein R^1 is methyl and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^6 and R^7 are hydrogen.

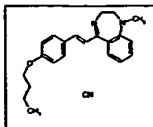
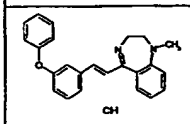
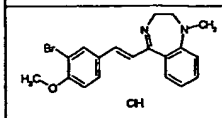
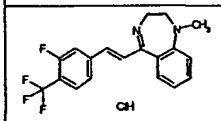
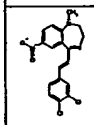
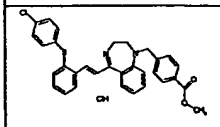
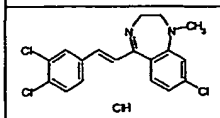
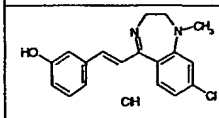
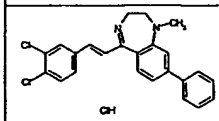
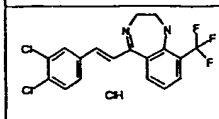
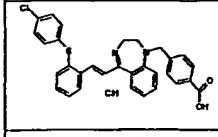
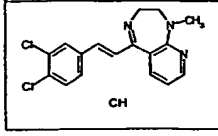
5. A compound of any one of claims 1 to 4 selected from

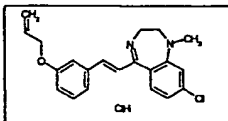
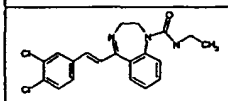
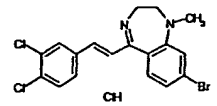
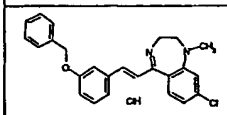
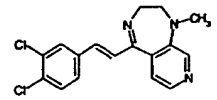
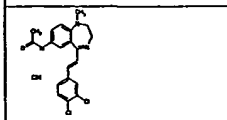
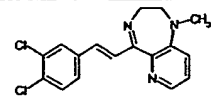
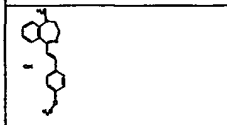
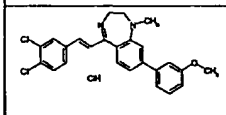
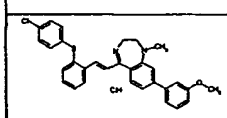
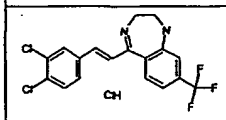
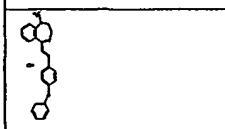
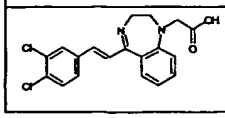
Table 1:

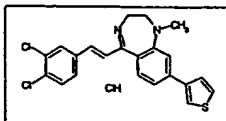
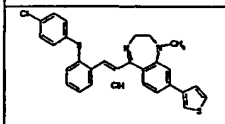
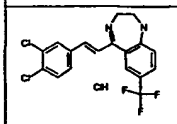
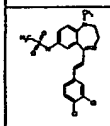
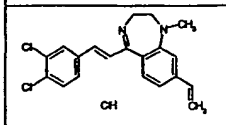
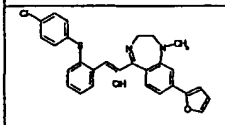
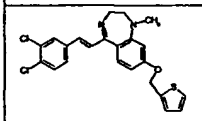
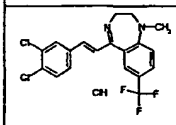
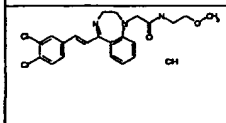
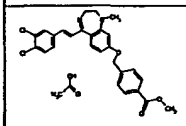
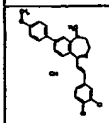
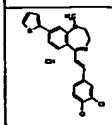
Structure	Names
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-2H-benzo-1,4-diazepin-2-one
	(E)-9-(3,4-Dichlorostyryl)-5,7-dihydro-6H-1,3-dioxolo [4,5-h][1,4]benzodiazepin-6-one
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-7,8-dimethoxy-2H-1,4-benzodiazepin-2-one
	(E)-5-(3,4-Dichlorostyryl)-1,3-dihydro-1-methyl-2H-benzo-1,4-diazepin-2-one
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-benzo-1,4-diazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-benzo-1,4-diazepine dihydrochloride
	(E)-1,3-Dihydro-5-styryl-2H-benzo-1,4-diazepin-2-one

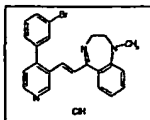
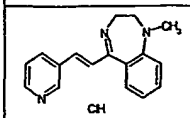
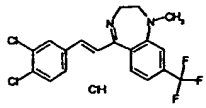
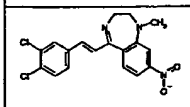
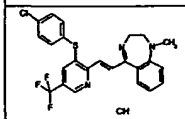
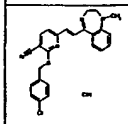
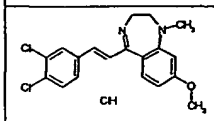
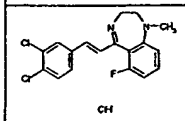
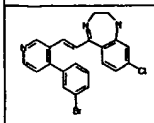
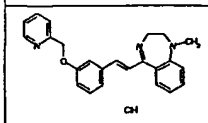
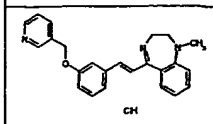
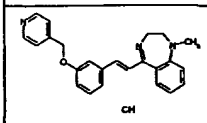
	(E)-5-(3,4-Dichlorostyryl)-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-propyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-1-Acetyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-styryl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-1-Benzoyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-1-Benzyl-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-ethanol hydrochloride
	(E)-5-(2,3-Dichlorostyryl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-(4-nitrobenzyl)-1H-1,4-benzodiazepine dihydrochloride
	Methyl (E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate dihydrochloride
	(E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-[(2-naphthyl)methyl]-1H-1,4-benzodiazepine dihydrochloride

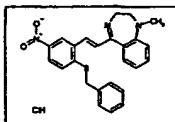
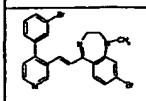
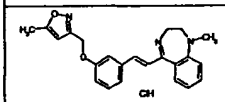
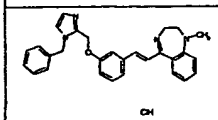
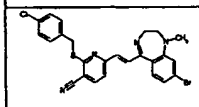
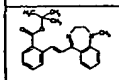
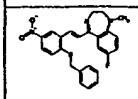
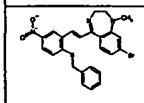
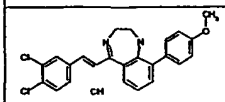
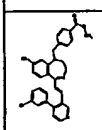
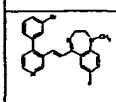
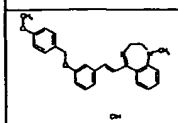
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-isopropyl-1H-1,4-benzodiazepine dihydrochloride
	Methyl (E)-3-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-3-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-ol hydrochloride
	tert-Butyl (E)-[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]carbamate
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-amine hydrochloride
	Methyl (E)-2-[[5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(tetrahydro-2(RS)- pyranyloxy)-1-methyl-1H-1,4-benzodiazepine
	(E)-2-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(tetrahydro-2(RS)-pyranyloxy)-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-6-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	Ethyl (E)-6-(3,4-dichlorostyryl)-4H-imidazo[1,5-a][1,4]benzo-diazepine-3-carboxylate

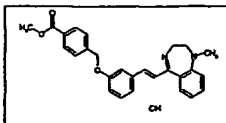
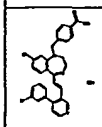
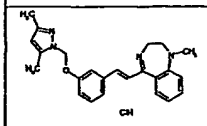
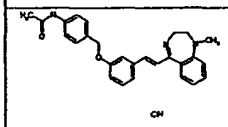
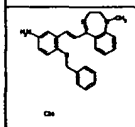
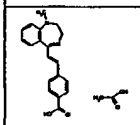
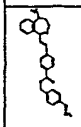
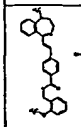
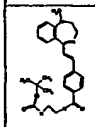
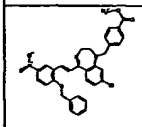
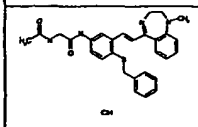
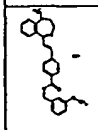
	(E)-5-(4-Butoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(3-phenoxystyryl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3-Bromo-4-methoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-Fluoro-4-(trifluoromethyl)styryl]-2,3-dihydro-1-methyl-1H-benzo[e][1,4]diazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-7-nitro-1H-1,4-benzodiazepine
	Methyl (E)-4-[[5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoate hydrochloride
	(E)-8-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-3-[2-(8-Chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl) vinyl]phenol hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-phenyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-9-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-4-[[5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[2,3-e][1,4] diazepine hydrochloride (1:3)

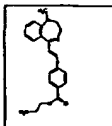
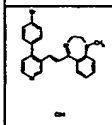
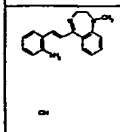
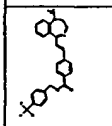
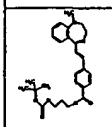
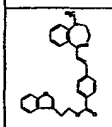
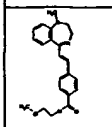
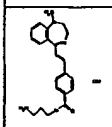
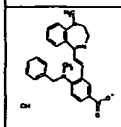
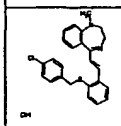
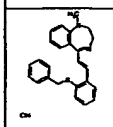
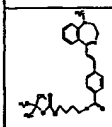
	(E)-5-(3-Allyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-N-ethyl-2,3-dihydro-1H-1,4-benzodiazepine-1-carboxamide
	(E)-8-Bromo-5-(3,4-dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3-Benzyloxystyryl)-8-chloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,4-e][1,4] diazepine
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-acetamide hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-pyrido[3,2-e][1,4] diazepine
	(E)-2,3-Dihydro-5-(4-methoxystyryl)-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(3-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-8-(3-methoxyphenyl) -1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(4-phenoxystyryl)-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine-1-acetic acid

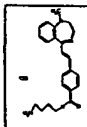
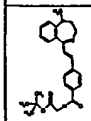
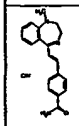
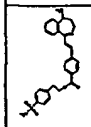
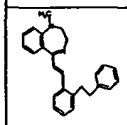
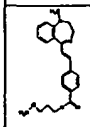
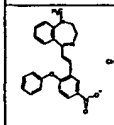
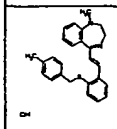
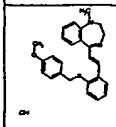
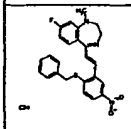
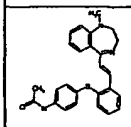
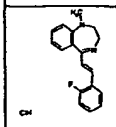
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(3-thienyl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1-methyl-8-(3-thienyl)- 1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-N-[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-7-yl]methanesulfonamide
	5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-vinyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenylthio)styryl]-8-(2-furyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thenyloxy)-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-7-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-N-(2-methoxyethyl)-1H-1,4-benzodiazepin-1-acetamide dihydrochloride
	Methyl (E)-4-[[5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-yloxy]methyl]benzoate acetate (1:2)
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-(4-methoxyphenyl)-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-(2-thienyl)-1H-1,4-benzodiazepine hydrochloride

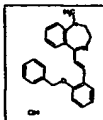
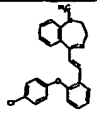
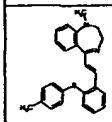
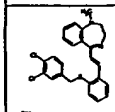
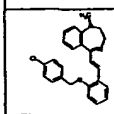
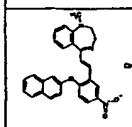
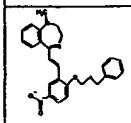
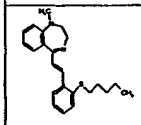
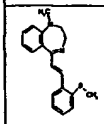
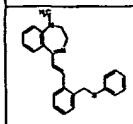
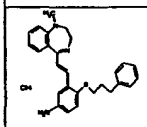
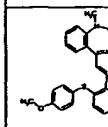
	(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(3-pyridyl)vinyl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-8-(trifluoromethyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-8-nitro-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-[3-(4-Chlorophenylthio)-5-(trifluoromethyl)-2-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2-(4-Chlorobenzylthio)-6-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-3-pyridinecarbonitrile dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-8-methoxy-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-6-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[3-[(2-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(3-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(4-pyridyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride

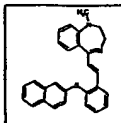
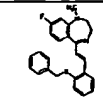
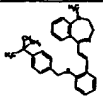
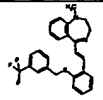
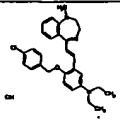
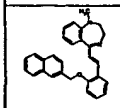
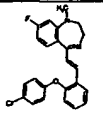
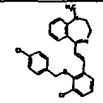
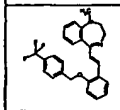
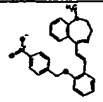
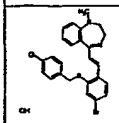
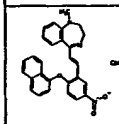
	(E)-5-(2-Benzylthio-5-nitrostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-8-Bromo-5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(5-methyl-3-isoxazol-3-yl)methoxy]styryl]- 1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-[(1-Benzyl-1H-imidazol-2-yl)methoxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-6-[2-(8-Bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-2-(4-chlorobenzylthio)-3-pyridinecarbonitrile dihydrochloride
	tert-Butyl (E)-2-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoate dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-8-bromo-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-(4-methoxyphenyl)-1H-1,4-benzodiazepine hydrochloride
	Methyl (E)-4-[[5-[2-[4-(3-bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate
	(E)-5-[4-(3-Bromophenyl)-3-pyridyl]-7-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2,3-Dihydro-3-(4-methoxybenzyloxy)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride

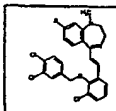
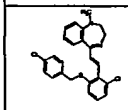
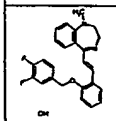
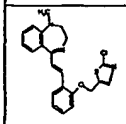
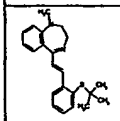
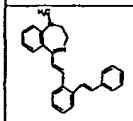
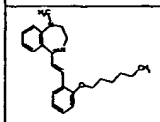
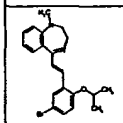
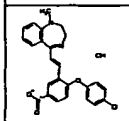
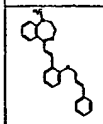
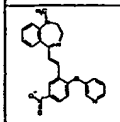
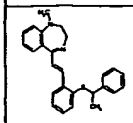
	Methyl (E)-4-[[3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenoxy]methyl]benzoate dihydrochloride
	(E)-4-[[5-[2-[4-(3-Bromophenyl)-3-pyridyl]vinyl]-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoic acid hydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[3-[(3,5-dimethyl-1-pyrazolyl)methoxy]styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-4'-[[3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenoxy]methyl]acetanilide hydrochloride
	(E)-4-Benzylthio-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzoic acid acetate (1:1)
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(4-methoxybenzyl)benzamide hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxybenzyl)benzamide hydrochloride
	tert-Butyl (E)-[2-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)-vinyl]-benzamido]ethyl)]carbamate
	Methyl (E)-4-[[5-(2-benzylthio-5-nitrostyryl)-8-chloro-2,3-dihydro-1,4-benzodiazepin-1-yl]methyl]benzoate
	(E)-2-Acetamido-4'-benzylthio-3'-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]acetanilide dihydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxybenzyl)benzamide hydrochloride

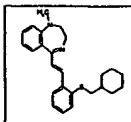
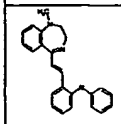
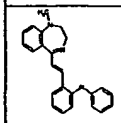
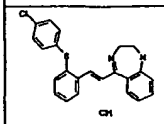
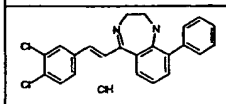
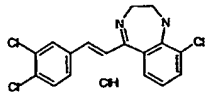
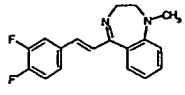
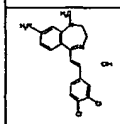
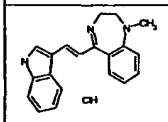
	(E)-N-(2-Aminoethyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-5-[2-[4-(4-Bromophenyl)-3-pyridyl]vinyl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]aniline hydrochloride
	(E)-N-[4-(Trifluoromethyl)benzyl]-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide
	tert-Butyl (E)-[3-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]propyl]carbamate
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(1H-indol-3-yl)ethyl]benzamide
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(2-methoxyethyl)benzamide
	(E)-N-(3-Aminopropyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-methyl-4-nitroaniline dihydrochloride
	(E)-5-[2-(4-Chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthiostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	tert-Butyl (E)-(4-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]butyl)carbamate

	(E)-N-(4-Aminobutyl)-4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	tert-Butyl (E)-[4-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamido]acetate
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]benzamide hydrochloride
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-[2-(4-sulfamoylphenyl)ethyl]benzamide
	(E)-2,3-Dihydro-1-methyl-5-[2-(2-phenylethyl)styryl]-1H-1,4-benzodiazepine
	(E)-4-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N-(3-methoxypropyl)benzamide
	(E)-2,3-Dihydro-1-methyl-5-(5-nitro-2-phenoxystyryl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(4-methylbenzylthio)-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-5-[2-(4-methoxybenzylthio)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthio-5-nitrostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-4'-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenylthio]acetanilide hydrochloride
	(E)-5-(2-Fluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride

	(E)-5-(2-Benzyloxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenoxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-(2-p-tolylthiostyryl)-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(3,4-Dichlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorobenzyloxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-phenylpropylthio)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-(2-pentylthiostyryl)-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-(2-methylthiostyryl)-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[2-(phenylthiomethyl)styryl]-1H-1,4-benzodiazepine
	(E)-3-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-4-(3-phenylpropylthio)aniline hydrochloride
	(E)-2,3-Dihydro-5-[2-(4-methoxyphenylthio)styryl]-1-methyl-1H-1,4-benzodiazepine dihydrochloride

	(E)-2,3-Dihydro-1-methyl-5-[2-(2-naphthylthio)styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(2-Benzylthiostyryl)-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-tert-Butyl-benzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[3-(Trifluoromethyl)benzylthio]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-4-(4-Chlorobenzyloxy)-3-[2-(2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]-N,N-diethylaniline dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-[(2-naphthyl)methoxy]-styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-(4-Chlorophenoxy)styryl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[3-Chloro-2-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[4-(Trifluoromethyl)benzyloxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(4-nitrobenzyloxy)styryl]-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[4-Bromo-2-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-2,3-Dihydro-1-methyl-5-[2-(1-naphthyloxy)-5-nitrostyryl]-1H-1,4-benzodiazepine dihydrochloride

	(E)-5-[3-Chloro-2-(3,4-dichlorobenzylthio)phenyl]-8-fluoro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-Chloro-6-(4-chlorobenzylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(E)-5-[2-(3,4-Difluorobenzyloxy)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-[2-[(2-Chloro-5-thiazolyl)methoxy]styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-[2-(tert-Butylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(all-E)-2,3-Dihydro-1-methyl-5-(2-styrylstyryl)-1H-1,4-benzodiazepine
	(E)-5-(2-Hexyloxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-(5-Bromo-2-isopropoxystyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-5-[2-(4-Chlorophenoxy)-5-nitrostyryl]-3,4-dihydro-1-methyl-1H-1,4-benzodiazepine hydrochloride
	(all-E)-2,3-Dihydro-1-methyl-5-[2-(styrylthio)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[5-nitro-2-(3-pyridyloxy)styryl]-1H-1,4-benzodiazepine
	(E)-2,3-Dihydro-1-methyl-5-[2-(1(RS)-phenylethylthio)styryl]-1H-1,4-benzodiazepine

	(E)-5-[2-(Cyclohexylmethylthio)styryl]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine
	(E)-N-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenyl]aniline
	(E)-N-[2-[2-(2,3-Dihydro-1-methyl-1H-1,4-benzodiazepin-5-yl)vinyl]phenyl]aniline
	(E)-5-[2-(4-Chlorophenylthio)styryl]-2,3-dihydro-1H-1,4-benzodiazepine hydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-9-phenyl-1H-1,4-benzodiazepine hydrochloride
	(E)-9-Chloro-5-(3,4-dichlorostyryl)-2,3-dihydro-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Difluorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine dihydrochloride
	(E)-5-(3,4-Dichlorostyryl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-8-amine hydrochloride
	(E)-2,3-Dihydro-5-[2-(1H-indol-3-yl)vinyl]-1-methyl-1H-1,4-benzodiazepine hydrochloride

or pharmaceutically acceptable salts thereof.

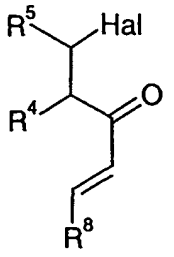
6. A compound or pharmaceutically acceptable salt of any one of claims 1 to 5 for use as a therapeutically active substance.

7. A compound or pharmaceutically acceptable salt of claim 6 for use in the treatment or prevention of an HPV mediated disease.

8. A medicament containing a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 together with a therapeutically inert carrier.

9. A medicament of claim 8 for use in the treatment or prevention of an HPV mediated disease.

10. Process for the preparation of a compound of formula (I) or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5, which process comprises coupling of a compound of formula



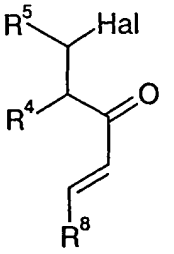
IV

wherein R^4 and R^5 are as above and Hal is a halogen atom
with a diamine of formula

$$R^1NH(CH_2CH_2)NH_2 \qquad V$$

wherein R^1 is as above.

11. Compounds of formula



IV

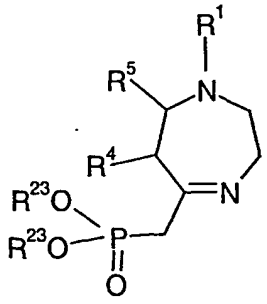
wherein R^4, R^5, R^8 and hal are as above.

12. Compounds of formula

$$R^1NH(CH_2CH_2)NH_2 \qquad V$$

wherein R^1 is as above.

13. Process for the preparation of a compound of formula (I) or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5, which process comprises coupling of a phosphoric acid ester of formula



VIII

wherein R^1, R^4 and R^5 are as above and wherein R^{23} is lower alkyl with an aldehyde of the formula

R^8CHO VII

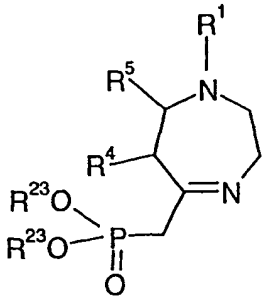
wherein R^8 is as above.

14. Compounds of formula

R^8CHO VII

wherein R^8 is as above.

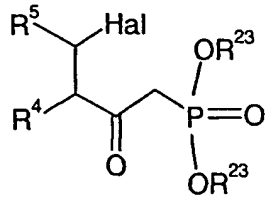
15. Compounds of formula



VIII

wherein R^1, R^4 and R^5 are as above and wherein R^{23} is lower alkyl.

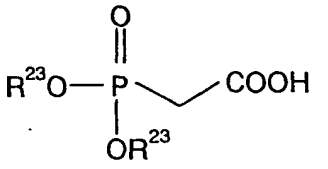
16. Compounds of formula



IX

wherein R^4, R^5, R^{23} and Hal are as above.

17. Compounds of formula



X

wherein R^{23} is as above.

18. A compound or pharmaceutically acceptable salt of any one of claims 1 to 5 when manufactured according to the process of claim 10 or 13 or according to process equivalent thereto.

19. A process for preparing a medicament, which process comprises bringing a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 into a galenical administration form together with a therapeutically inert carrier.

20. Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 for the treatment or prevention of an HPV mediated disease.

21. Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 for the preparation of a medicament containing a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 for the treatment or prevention of an HPV mediated disease.

22. A method of treating or preventing an HPV mediated disease in a subject, which method comprises administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1 to 5.

23. Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 5 for the manufacture of a medicament for the treatment or prevention of an HPV mediated disease.

24. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/EP 01/06895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D243/14 C07D401/06 C07D403/06 C07D471/04 C07D401/12
C07D417/12 C07D413/12 C07D403/12 C07D487/04 A61K31/5513
A61K31/5517 A61K31/5517 //(C07D471/04,243:00,209:00),
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 350 131 A (DUPHAR INT RES) 10 January 1990 (1990-01-10) see general formula and examples 26 and 48 and page 6, lines 1-23 ---	1,2,4,6, 8,10,18, 19
A	US 3 426 014 A (SCHMITT JOSEF) 4 February 1969 (1969-02-04) the whole document ---	1-10,13, 15,18-24
A	EP 0 462 522 A (HOFFMANN LA ROCHE) 27 December 1991 (1991-12-27) the whole document ---	1-10,13, 15,18-24
A	WO 00 12547 A (DEPLA ERIK ;INNOGENETICS NV (BE); MAERTENS GEERT (BE); MOEREELS HE) 9 March 2000 (2000-03-09) see especially formula I --- -/--	1-10,13, 15,18-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2001	12. 12. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern I Application No
PCT/EP 01/06895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D487/04,243:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 14063 A (HUGHES E JOHN L ;BERNARD HANS ULRICH (SG); TING ANTHONY EUGENE (SG) 16 March 2000 (2000-03-16) the whole document	1-10,13, 15,18-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2001	9 7. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern d Application No
PCT/EP 01/06895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ZA 9104202 A	25-03-1992

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/EP 01/06895

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10, 13, 15, 18-24

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,13,15,18-24

   Compounds of the formula I, processes for their preparation, uses thereof and the intermediate compounds of formula VIII, used in their preparation according to claim 13.

2. Claim : 11

   Intermediates of the formula IV

3. Claim : 12

   Intermediates of the formula V

4. Claim : 14

   Intermediates of the formula VII

5. Claim : 16

   Intermediates of the formula IX

6. Claim : 17

   Intermediates of the formula X

INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/EP 01/06895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BR 9913226 A	22-05-2001
		CN 1315963 T	03-10-2001
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		WO 0014063 A1	16-03-2000
		EP 1112250 A1	04-07-2001